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Preoperative Computed Tomography Imaging of the Pancreas Identifying Predictive Factors for the Progression of Grade A, or Biochemical Leak, to Grade B Postoperative Pancreatic Fistula Following Pancreaticoduodenectomy: A Retrospective Study

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This retrospective study aimed to identify the predictive factors for the progression of grade A, or early biochemical leak, to grade B postoperative pancreatic fistula (POPF) following pancreaticoduodenectomy using preoperative computed tomography (CT) imaging of the pancreas.





Material/Methods: A total of 156 patients were analyzed retrospectively. Biochemical leakage occurred in 60 patients, who were divided into POPF progression and non-POPF progression groups. Perioperative parameters were collected. Univariate analysis and multivariate logistic regression analysis were done. For the parameters with statistical significance, the area under the curve (AUC) was calculated if possible and the predictive value was assessed.

Results: Univariate analysis showed that main pancreatic duct diameter, postoperative complications (except POPF), prothrombin time (PT) and serum albumin on postoperative day 3, and pancreatic CT value were risk factors of POPF ($P < 0.05$). Multivariate analysis showed that serum albumin and PT on postoperative day 3 and pancreatic CT value were independent risk factors of POPF ($P < 0.05$). Lower postoperative albumin, lower pancreatic CT value, and longer PT were associated with a higher risk of POPF ($P < 0.05$). The AUC of CT value was 0.808. CT value thresholds of 42.5 Hounsfield units (HU) and 41.5 HU were tied for the highest predictive performance, with Youden indices of 0.486 for both, and sensitivity of 79% and 71%, and specificity of 69% and 78%, respectively.

Conclusions: Preoperative laboratory investigations and CT imaging of the pancreas may identify factors associated with early biochemical leakage progressing to grade B POPF following pancreaticoduodenectomy.

Keywords: **Cone-Beam Computed Tomography • Pancreatic Fistula • Pancreaticoduodenectomy • Postoperative Complications**

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 3186  3  1  30



Background

Pancreaticoduodenectomy is considered one of the most complex and challenging operations owing to the massive dissection and resection required [1-3]. However, this surgery is currently regarded as safe and reliable for the treatment of pancreatic tumors and chronic pancreatitis [4]. Experienced surgeons know how to choose the correct method of resection and reconstruction. Standardized resection procedures are well established and can be carried out in high-volume institutions with a morbidity and mortality rate of less than 5% [5]. One of the most important and harmful complications of the resection is postoperative pancreatic fistula (POPF) [6,7], which has an incidence rate of 3% to 30% [8].

According to the definition and grading of the International Study Group in Pancreatic Surgery (ISGPS), grade A POPF, also called biochemical leak, is not considered a true pancreatic fistula or an actual complication; rather, POPF associated with the incidence of clinically relevant pancreatic fistula is regarded as grade B or C [9,10]. More attention should be given to the possibility of patients with biochemical leaks progressing to grade B pancreatic fistula after surgery [11]. Some researchers suggested that data from computed tomography (CT) imaging before surgery might provide useful information about the risk of POPF [12-14]. Therefore, in this retrospective study, we aimed to identify the predictive factors for the progression of grade A, or early biochemical leak, to grade B postoperative pancreatic fistula (POPF) following pancreaticoduodenectomy using preoperative CT imaging of the pancreas.

Material and Methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Second People's Hospital of Yibin, Sichuan, China (approval No. 2020-115-01). Written informed consent was obtained from all patients.

Patient Enrollment

A total of 156 consecutive patients underwent pancreaticoduodenectomy from 2015 to 2019 for periampullary diseases at the Second Hospital of Yibin City. There were 104 men and 52 women, with an average age of 62 ± 7 years (range, 37-77 years). Among the 156 patients, 60 experienced postoperative biochemical leakage, of which 24 progressed to grade B pancreatic fistula, without grade C pancreatic fistula. All enrolled patients received surgical treatment, and all operations were performed by the same surgical team to minimize differences in surgical experience and technique. After surgery, routine therapy was applied, such as short-term feeding restriction,

parenteral nutrition support, symptomatic therapy, and postoperative drainage tube unblocking. The results of postoperative pathological examination were used to determine whether the patients' tumors were benign or malignant.

Study Design

This investigation was a clinical retrospective study. Patients who had biochemical leaks were divided into 2 groups: the POPF progression group and the non-POPF progression group. All related preoperative, intraoperative, and postoperative parameters were collected and recorded to identify the risk factors of progression from biochemical leak to grade B pancreatic fistula.

Surgical Technique

All patients underwent conventional Whipple surgery after tracheal intubation and general anesthesia. Pancreaticoduodenectomy and lymph node dissection were performed. The Child's method was used to reconstruct the digestive tract. End-to-side anastomosis of the pancreatic duct and jejunum mucosa was performed in all patients. The pancreatic stump was meshed with 4-0 Prolene suture at a distance of 0.5 to 1.0 cm from the pancreatic section. A continuous suture was applied from the posterior margin tissue to the jejunum line of the mesangial limbus serosa. Then, the seromuscular layer of the jejunum was cut at the corresponding pancreatic stump and pulled to both sides to expose an area with the size equivalent to the pancreatic stump. Thus, an area of the jejunum mucosa layer, with a size equivalent to the pancreatic stump, was exposed and a small hole was opened, with the diameter equal to that of the pancreatic duct. According to the diameter of the pancreatic duct, a supportive drainage tube of appropriate size was placed and sutured in the duct. The pancreatic duct and the posterior wall of the jejunal mucosa were sutured continuously for 3 to 4 stitches, and then the supportive tube of the pancreatic duct was inserted into the jejunum. The distal end of the supportive tube passed through the anastomosis between the duct and the jejunum. Then, the pancreatic duct and the anterior wall of the jejunum mucosa were sutured continuously with 3 to 4 stitches and the anterior margin of the pancreatic stump was sutured continuously with the serosamus layer of the jejunum at a distance of 0.5 to 1.0 cm from the pancreatic section.

Definitions

The International Study Group on Pancreatic Fistula (ISGPF) developed the definition and grading of POPF, which has been commonly accepted and used by clinicians. Biochemical leakage is defined as a drain output of any measurable volume of fluid with an amylase level >3 times the upper limit of the normal

serum amylase range. Grade B POPF is defined more strictly. Biochemical leakage combined with any of the following 5 conditions is defined as grade B POPF: (1) peritoneal drainage tubes indwelling >3 weeks; (2) clinical changes in postoperative management; (3) the pancreatic fistula requires repositioning by endoscopic or percutaneous procedures; (4) bleeding requires postoperative treatment of angiography; or (5) the pancreatic fistula causes infection, without organ failure [9].

Some research groups have extensively analyzed CT images of the pancreas and have identified many variables that are significantly associated with POPF [12-14]. The diameter of the main pancreatic duct (MPD) and the CT value of the pancreatic body are the independent components derived from CT images. In our study, the diameter of the MPD and the CT value of the pancreatic body were independently measured by the same radiologist before surgery. The diameter of the MPD was measured at the section where maximal ductal dilatation was noted on CT. When measuring the CT value of the pancreatic body, the radiologist avoided all pancreatic tumors, calcifications, ducts, blood vessels, and non-pancreatic tissue. The CT value was measured 3 times for each patient, and the average of the results was taken as the final CT value of the patient's pancreatic body.

Statistical Analysis

SPSS v.25.0 for Microsoft Windows (IBM) statistical software package was used to conduct all statistical analyses. The data were expressed as the mean and standard deviation for continuous variables or median (interquartile range) for the frequency of categorical variables. Univariable analyses were performed by *t* test for continuous variables. Pearson's chi-square test, MannWhitney U test, or Fisher's exact test was used to compare categorical variables, as appropriate. All variables with $P < 0.05$ were subjected to multivariate analysis, which was performed by binary logistic regressions to identify the independent variables associated with POPF. The odds ratio (OR) and its 95% confidence interval were reported. A *P* value less than 0.05 indicated statistical significance.

Results

A total of 156 patients underwent pancreaticoduodenectomy. After the surgery, 60 patients had biochemical leak, and, of them, 24 patients experienced significant POPF (grade B). The median age of the 60 patients was 62 years (range, 49-74 years) and 31 were men (51.7%). The non-POPF progression group received routine therapy including short-term feeding restriction, parenteral nutrition support, liver protection, postoperative drainage tube unblocking, and symptomatic therapy. The POPF progression group received an intensive treatment

including rational use of antibiotics, extended drainage time, percutaneous peritoneal drainage, and angiographic procedures to detect bleeding. All patients ($n=60$) were discharged from the hospital.

According to the results of the univariate analyses, the risk factors associated with progression from biochemical leak to grade B fistula were MPD diameter, postoperative complications (except POPF), prothrombin time (PT) on postoperative day 3, serum albumin on postoperative day 3, and the preoperative CT value of the pancreatic body ($P < 0.05$). However, there were no differences in age, sex, body mass index, total bilirubin, albumin, alanine aminotransferase, operation time, or intraoperative blood loss ($P > 0.05$) (Table 1). Then, multivariate analysis was conducted on MPD diameter, postoperative complications (except POPF), PT on postoperative day 3, serum albumin on postoperative day 3, and the CT value of the pancreatic body, with the results showing that CT value (OR, 0.611, $P=0.012$), PT on postoperative day 3 (OR, 2.955, $P=0.032$), and serum albumin on postoperative day 3 (OR, 0.607, $P=0.022$) were independent risk factors of progression from biochemical leak to grade B pancreatic fistula (Table 2). Higher postoperative PT and lower CT values and postoperative albumin were associated with a higher risk of progression to grade B pancreatic fistula.

A receiver operating characteristic (ROC) curve was drawn to detect the relationship between a preoperative pancreas plain CT value and grade B POPF (Figure 1). When the area under the curve (AUC) ≥ 0.5 and < 1 , the larger the AUC was, the greater the predictive value was. When AUC < 0.5 , it did not have predictive value. Generally, when the AUC ≥ 0.5 and < 0.7 , it had low predictive value; when the AUC ≥ 0.7 and < 0.9 , it had medium predictive value; and when the AUC < 0.9 , it had high predictive value. The AUC of preoperative pancreatic plain CT values was 0.808, with medium predictive value. Table 3 shows that with the increase of the cutoff CT value, the true positive rate gradually increased and the false negative rate decreased, and the true negative rate decreased and the false positive rate increased. Cutoff CT values of 42.5 Hounsfield units (HU) and 41.5 HU achieved 79.2% and 70.8% sensitivity and 69.4% and 77.8% specificity, respectively. These 2 cutoffs were tied for the highest predictive performance, with a Youden index of 0.486.

Discussion

The results of this research show that the albumin level on day 3 after pancreaticoduodenectomy was an independent predictor of prognosis after the surgery, and the albumin level on day 3 after the surgery might predict whether or not biochemical leakage progressed to grade B pancreatic fistula after

Table 1. Univariate analysis of risk factors for progression from biochemical leak to grade B pancreatic fistula.

Variable	Postoperative pancreatic fistula (POPF) progression		χ^2	P value
	Yes	No		
Sex				
Male	15 (62.5%)	16 (44.4%)	1.880	0.170
Female	9 (37.5%)	20 (55.6%)		
Age (yr)*	62.5±5.0	62.3±5.8	0.345	0.856
BMI (kg/m ²)**	24.60 (2.65)	24.60 (3.00)	0.955	0.683
PT (s)**	12.60 (1.4)	12.60 (1.2)	0.598	0.833
Serum albumin (g/L)**	35.40 (2.6)	35.90 (2.4)	0.996	0.752
Preoperative total bilirubin* (µmol/L)				
≥171	11 (45.8%)	13 (36.1%)	0.567	0.451
<171	13 (54.2%)	23 (63.9%)		
Preoperative ALT (U/L)*	76.5±14.0	72.7±13.3	0.582	0.295
Preoperative CT value* (HU)	40.1±2.7	43.9±3.4	0.426	0.0001
MPD (mm)				
≥3	8 (33.3%)	24 (66.7%)	6.429	0.011
<3	16 (66.7%)	12 (33.3%)		
Operative time (min)*	366.3±20.9	358.0±23.9	0.370	0.177
Blood loss (ml)				
≥600	12 (50.0%)	22 (61.1%)	0.724	0.395
<600	12 (50.0%)	14 (38.9%)		
Postoperative PT (s)*	16.4±1.3	14.8±1.2	0.879	0.0001
Postoperative serum albumin (g/L)*	29.6±2.4	33.2±2.5	0.723	0.0001
Postoperative total bilirubin (µmol/L)*				
≥171	9 (37.5%)	10 (27.8%)	0.629	0.428
<171	15 (62.5%)	26 (72.2%)		
Postoperative ALT (U/L)*	54.4±9.9	52.2±5.9	0.166	0.302
Postoperative complication				
Yes	5 (20.8%)	1 (3.0%)	5.216	0.022
No	19 (79.2%)	35 (97.0%)		
Pathological type of tumour				
Benign tumour	0 (0.0%)	1 (2.8%)	0.753	0.686
Low grade malignant tumour	1 (4.2%)	1 (2.8%)		
High grade malignant tumour	23 (95.8%)	34 (94.4%)		

yr – years old; postoperative – on postoperative 3 days; BMI – body mass index; PT – prothrombin time; ALT – alanine aminotransferase; MPD – main pancreatic duct. HU – Hounsfield Unit. * Values are mean±standard deviation; ** median (interquartile range).

Table 2. Multivariate logistic regression analysis of factors for progression from biochemical leak to grade B pancreatic fistula.

Value	B	SE	Wals	P value	OR	95% CI
Postoperative serum albumin (g/L)	-0.499	0.218	5.257	0.022	0.607	0.396–0.930
MPD (mm)	0.049	0.927	0.003	0.958	1.051	0.171–6.467
Postoperative complication	2.500	1.716	2.123	0.145	12.188	0.422–352.063
Postoperative PT (s)	1.084	0.504	4.617	0.032	2.955	1.100–7.941
Preoperative CT value (HU)	-0.493	0.197	6.248	0.012	0.611	0.415–0.899

Postoperative – on postoperative 3 days; PT – prothrombin time; MPD – main pancreatic duct; CT – computed tomography; HU – Hounsfield Unit.

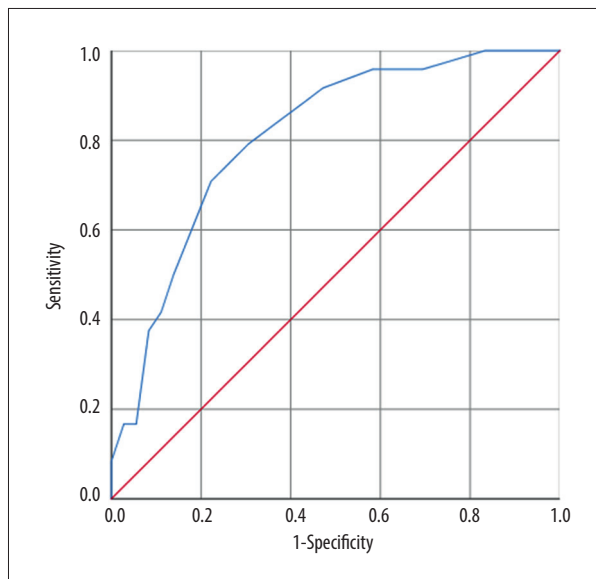


Figure 1. Receiver operating characteristic (ROC) curve was drawn based on computed tomography (CT) value of pancreatic body.

surgery. As the albumin level decreased after surgery, the risk of developing into grade B pancreatic fistula POPF increased (OR=0.607, 95% CI=0.396-0.930, $P=0.022$). Some researchers suggest that serum albumin could be used as a common parameter to reflect metabolism and nutritional status, which means it is valuable to predict patient prognosis after pancreaticoduodenectomy [15]. Fujiwara et al [16] thought that a certain concentration of serum albumin could suppress the systemic inflammatory response, while a lower concentration of serum albumin did not have such a function and would bring about immunonutrition disorders and raise the risk of postoperative complications such as POPF. Utsumi et al reported that the higher the controlling nutritional status scores, the higher risk of POPF the patients face [13]. In the present study, there was no significant difference in the patients' albumin levels before the pancreaticoduodenectomy, so we believed that the nutrition status among patients was nearly at the same level. However, there was an obvious difference in albumin levels

among the patients after surgery. The possible reason might be that some disorders occurred in nutrition and metabolism, or the patients had insufficient nutrition, which resulted in the low ability of tissue healing and anastomotic stoma healing. Therefore, they were at risk of developing POPF [17]. Meanwhile, low albumin levels were related to poor liver function. Hypoalbuminemia could easily bring about inflammation, and inflammation in the anastomotic stoma could also have a negative impact on tissue recovery. Therefore, timely replenishment of albumin and regularly monitoring its level could reduce the incidence of pancreatic fistula.

In the present study, the PT value (OR=2.955, 95% CI=1.100-7.941, $P=0.032$) on the third day after surgery was also an independent prognostic predictor of progression from biochemical leak to grade B pancreatic fistula. We considered that PT was an index related to blood coagulation and prolonged PT meant exogenous blood coagulation dysfunction. Surgical trauma caused the exposure of tissue factor and the activation of the X factor. This activated the access to exogenous blood coagulation and consumed a large amount of coagulation factors. Meanwhile, patients with surgical trauma generally had high fibrinolysis, which weakened coagulation function, and thus the risk of bleeding increased. The liver function of some patients was damaged, probably due to surgical trauma, excessive intraoperative hemorrhage, or obstructive jaundice, which resulted in the excessive consumption of blood coagulation factor and the limitation of its productivity. Due to the coagulation disorder after pancreaticoduodenectomy, the coagulation function was weakened, which increased the chance of pinhole leakage around the pancreaticojejunostomy and local hematoma. This was not beneficial for the healing of the anastomosis and could easily have caused pancreatic fistula and intra-abdominal infection. Bassi et al [18] reported that pancreatic fistula is the main cause of late hemorrhage after pancreaticoduodenectomy. Abdominal bleeding usually occurs 5 to 10 days after surgery, which increases patient mortality. Therefore, for patients with bleeding in the first week after surgery, erosion in the main blood vessels should be suspected, and corresponding positive measures should be taken [19].

Table 3. Preoperative computed tomography (CT) value of the pancreatic body in the sensitivity and specificity for identifying progression from biochemical leak to grade B pancreatic fistula.

CT value as the cut-off point	The sensitivity	The specificity	Youden index
35.0	0.00	1.00	0.000
36.5	0.08	1.00	0.083
37.3	0.17	0.97	0.139
37.8	0.17	0.94	0.111
38.5	0.38	0.92	0.292
39.5	0.42	0.89	0.306
40.5	0.50	0.86	0.361
41.5	0.71	0.78	0.486
42.5	0.79	0.69	0.486
43.5	0.92	0.53	0.445
44.5	0.96	0.42	0.375
45.5	0.96	0.31	0.264
46.5	1.00	0.17	0.167
47.5	1.00	0.11	0.111
49.0	1.00	0.08	0.083
50.5	1.00	0.06	0.056
52.0	1.00	0.00	0.000

CT – computed tomography.

At present, and based on extensive research, the texture of the pancreas is considered to be an independent predictor of postoperative pancreatic fistula. If the texture is softer, the patient is at higher risk of POPF [20]. However, this factor could not be tested in the preoperative comprehensive discussion and patient consultation. At the same time, different surgeons make their own subjective judgments about the texture of the pancreas by touching it with their fingers. In recent years, some studies have confirmed that that preoperative CT scans have the value of predicting POPF [21,22], and some research suggested that the number of CT scans of the pancreas was related to the density of the pancreas and suggested pancreatic fibrosis [23,24]. In addition, Kusafuka et al reported that a pancreas-visceral fat CT value ratio ≥ -0.40 and a serrated-type pancreas might indicate a high risk of POPF [14]. To standardize the judgement of pancreatic texture, the preoperative plain CT scan was chosen as the index in this study. The risk of progressing to grade B pancreatic fistula was predicted by measuring the number of preoperative CT scans. Our results showed that the pancreatic CT value was also an independent predictor of progressing to grade B pancreatic fistula, and for the patients with postoperative biochemical leak, the lower preoperative CT number they had, the more easily they would develop to grade B pancreatic fistula. Meanwhile, the ROC of the number of preoperative pancreas plain CT scans was generated according to whether the biochemical leak would

develop to grade B pancreatic fistula or not. It was discovered that $0.7 \leq \text{AUC} < 0.9$ had a medium value of prediction. When the CT number was 41.5 HU or 42.5 HU, the correct index was the most effective. However, the sample size was small in this study. Further research is needed to determine whether the preoperative CT number can be regarded as the judging index.

At present, a thinner pancreatic duct is recognized as an independent predictor of the prognosis of pancreaticoduodenectomy. The reason may be that the dilated pancreatic duct is related to pancreatic fibrosis. The fibrosis hardens the pancreas and thickens the pancreatic duct, resulting in a low incidence of fistulas after pancreaticoduodenectomy [25]. The thin pancreatic duct is not conducive to anastomosis and drainage of pancreatic juice, which increases the risk of POPF. Tomohisa Yamamoto et al [26] believe that a soft pancreatic texture and a pancreatic duct ≤ 3 mm in diameter are independent predictors of prognosis after pancreaticoduodenectomy, stating that the soft pancreas and narrow diameter of the duct indicates that pancreatic exocrine function is close to normal. Further, the secretion of pancreatic juice increases after pancreatectomy, while the risk of pancreatic fistula increases as well. Unfortunately, the results of our present study did not confirm that a pancreatic duct diameter ≤ 3 mm was an independent predictor of POPF prognosis. This may have resulted from the placement of pancreatic duct stents in most patients during

the operation of the end-to-side anastomosis of the pancreatic duct and mucous membrane. The placement of pancreatic duct stents in our study, to a certain extent, alleviated the problem of obstructed drainage caused by the narrow diameter of the pancreatic duct.

Six patients experienced other complications after pancreaticoduodenectomy. Five patients were in the POPF progression group; 4 patients had early abdominal hemorrhage and 1 had abdominal infection. One patient had early abdominal hemorrhage in the non-POPF progression group. Zhang et al [27] reported that POPF is closely related to other main complications such as peritoneal abscess, sepsis, postponement of stomach emptying, and hemorrhage. We considered that postoperative early abdominal hemorrhage might be associated with incomplete hemostasis during surgery, blood coagulation dysfunction, and bleeding at the anastomotic stoma. We also considered that abdominal infection was associated with pancreas fistulas and biliary fistulas. Nevertheless, the results of the analysis were not statistically significant. To a large extent, this was due to insufficient specimens. The patients who were enrolled in the present study underwent surgery with the routine Whipple procedure and underwent excision of the pancreas duodenum and lymph node dissection. Digestive tract reconstruction was conducted based on the Child's procedure. End-to-side anastomosis of the pancreatic duct and jejunum mucosa was performed in all patients. The surgery was completed with the cooperation of 2 teams led by 2 experienced surgeons, and so the suturing of the pancreas was not analyzed. Although there are many standardized anastomosis techniques available at present, there is no evidence that one anastomosis technique is better than another [28]. Also, the variable of operation time was analyzed, and the results showed no statistical significance. Kinaci et al [29] reported that there is no correlation between the operation time and prediction of POPF. However, Kim et al [30] suggested that an operation time of more than 300 min is an independent risk factor for grade B.

There are some limitations in this study. First, the sample size was small and patients with pancreatic fistula progressing to grade C from grade B were not enrolled, and therefore not discussed. Second, this was a retrospective, single-center study, and there may be selection bias of patients for pancreaticoduodenectomy. Third, the study investigators were the surgeons, which could have introduced bias. Finally, the postoperative pancreatic fistula risk score for patients were not performed in this study. Therefore, further studies with larger sample size, multiple centers, and postoperative pancreatic fistula risk scores are required to identify predictive factors for the progression of grade A, or biochemical leak, to grade B postoperative pancreatic fistula following pancreaticoduodenectomy.

Conclusions

In summary, the postoperative PT and albumin on day 3 after surgery can predict the progression to grade B pancreas fistula, according to our results. In the early period after surgery, more attention should be given to patients with abnormal coagulation function and low serum albumin, relevant indicators should be reviewed regularly, and corresponding symptomatic treatment could be given. The preoperative pancreas plain CT scan should be analyzed, and the CT number value should be studied instead of the texture of the pancreas. Such standardized judgement of pancreatic texture could be effective in predicting grade B POPF. When the CT number is 41.5 HU to 42.5 HU according to the generated ROC, biochemical leak has a high risk of developing into grade B pancreas fistula. Therefore, preoperative laboratory investigations and CT imaging of the pancreas may identify factors associated with grade A, or early biochemical leak, progressing to grade B POPF following pancreaticoduodenectomy.

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