A Novel Postoperative Inflammatory Score Predicts Postoperative Pancreatic Fistula After Pancreatic Resection

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Abstract. *Aim: The aim of this study was to characterize a high-risk group of patients for pancreatic fistula (PF) after pancreatic resection using postoperative clinical variables of patients. Patients and Methods: The retrospective study included 297 patients who underwent pancreatic resection between January 2001 and December 2011. We examined the relationship between perioperative findings and the incidence of postoperative PF (POPF) among patients who underwent pancreatic resection between 2001 and 2009 (early period). Next, patients were stratified into three groups using serum albumin and CRP on postoperative day 1 (score 0: albumin ≥2.7 g/dl and CRP ≤10 mg/dl; score 1: albumin <2.7 g/dl or CRP >10 mg/dl; score 2: albumin <2.7 g/dl and CRP >10 mg/dl) as postoperative inflammatory score (PIS). We examined perioperative findings including PIS and POPF among patients who underwent pancreatic resection between 2010 and 2011 (late period). Results: In univariate and multivariate analyses, male gender (p=0.032), serum albumin on postoperative day 1 (p=0.024) and serum CRP on postoperative day 1 were identified as independent risk factors for POPF in early-period patients. In univariate and multivariate analyses, postoperative hospital stay (p=0.009) and PIS (score 1: p=0.005, score 2: p=0.017) were identifical as independent risk factors for POPF in late-period patients. Conclusion: We found a novel PIS to indicate risk for PF after elective pancreatic resection.*

Despite recent advances in surgical procedures and postoperative management techniques, the morbidity rate after pancreatic resection remains high (1-4). Pancreatic fistula (PF) is the most frequent serious complication after pancreatic resection with an incidence varying from 5% to 25% (5, 6), and is reportedly associated with a high incidence of life-threating complications such as intra-abdominal abscess, intra-abdominal bleeding and sepsis (6, 7). Moreover, the occurrence of PF and pulmonary complications, among others lead to prolonged hospital stay. Previous reports have evaluated the perioperative factors that influence the incidence of postoperative PF (POPF), such as soft pancreatic parenchyma, narrow main pancreatic duct, intraoperative blood loss, blood transfusion, and operation time (5, 8-10). Therefore, it is important to identify patients with an increased risk of postoperative PF.

Prediction of surgical risk by evaluation of perioperative inflammatory status can be useful in the search for a strategy to prevent postoperative complications. Recent studies have indicated that perioperative systemic inflammatory responses can predict postoperative complications in various types of cancer (11-13). However, the relationship between these clinical risk factors and the incidence of postoperative PF remains unclear.

We hypothesized that the inflammatory response might be related to the development of PF after pancreatic resection. In this study we retrospectively investigated perioperative clinical variables as predictors of postoperative PF. Moreover, we developed a novel postoperative inflammatory score (PIS) using postoperative serum albumin and C-reactive protein (CRP) as independent risk predictors for the development of PF in patients after elective pancreatic resection.

Patients and Methods

Between January 2001 and December 2011, 301 patients underwent pancreatic resections for various primary diseases at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Out of these, four patients were excluded because of total pancreatectomy in three and lack of data in one, leaving the remaining 297 patients (181 males and 116 females; mean age=63.4 years, range=13-86 years) for this study. The patients underwent pancreaticoduodenectomy (n=199), pylorus-preserving duodenopancreatectomy (n=13), duodenum-preserving pancreatic head resection (n=1), distal pancreatectomy (n=77), middle pancreatectomy (n=1) and partial resection (n=6).

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Pancreatic fistula was defined by the guideline of the International Study Group on Pancreatic Fistula (ISGPF) (14). Pancreatic fistula is classified into three categories by ISGPF as follows: transient pancreatic fistula (no clinical impact) (grade A); requiring a change in management or adjustment in the clinical pathway (grade B); requires a major change in clinical management or deviation from the normal clinical pathway (grade C). In this study, grade B and C are defined as "postoperative PF)". Hemogram and chemistry profile were routinely measured for each patient preoperatively and on postoperative day 1.

Firstly, for the assessment of perioperative immune response, we investigated the relation between clinical variables and PF after pancreatic resection by univariate and multivariate analyses using patients treated in the early period (n=208, between January 2001 and December 2009). The following 23 factors were studied: age, gender, postoperative hospital stay, type of diseases, preoperative biliary drainage, type of resection (pancreaticoduodenectomy group and non-pancreaticoduodenectomy group), duration of operation, intraoperative blood loss, perioperative transfusion of red blood cell (RCC) or fresh-frozen plasma (FFP), concominant resection of the portal vein or other organs excluding the spleen, cardiovascular disease, arterial hypertension, diabetes mellitus, body-mass index (BMI), texture of the pancreatic parenchyma, and pre- and postoperative lymphocyte counts, serum amylase, serum albumin, and serum CRP values.

We then developed a novel PIS using postoperative serum albumin and CRP in order to characterize a high-risk group for postoperative PF. We analyzed patient characteristics in relation to PF after pancreatic resection in late period patients (n=89; between January 2010 and December 2011), using the following 22 factors: age, gender, postoperative hospital stay, type of disease, preoperative biliary drainage, type of resection, duration of operation, intraoperative blood loss, perioperative transfusion of RCC or FFP, concominant resection, cardiovascular disease, arterial hypertension, diabetes mellitus, BMI, texture of the pancreatic parenchyma, pre- and postoperative lymphocyte counts, serum amylase, serum albumin, serum CRP, and PIS (score 0, score 1 and score 2).

This study was approved by the Ethics Committee of the Jikei University School of Medicine. (21-121)

Statistical analysis. Data were expressed as the mean±standard deviation (SD). Univariate analyses were performed using Mann-Whitney's *U*-test, or Chi-square test. Multivariate analyses were performed using logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was performed to estimate the cutoff for PF after pancreatic resection. To determine the cutoff, we analyzed the point of intersection of the ROC curve and a 45-degree line crossing from the upper right to the lower left corner and detected the intersection point closest to the left upper corner. The software package SPSS (version 20; IBM SPSS Statistics®, Tokyo, Japan) was used for statistical analysis. All *p*-values were considered statistically significant when the associated probability was less than 0.05.

Results

Association between postoperative PF and perioperative factors among patients in the early period after pancreatic resection. The indications for pancreatic resection are summarized in Table I. The associations between postoperative PF and perioperative factors among early-period patients are outlined in Table II and Table III. In univariate analysis, male gender (p=0.020), postoperative hospital stay (p<0.001), preoperative biliary drainage (p=0.019), type of resection (p=0.033), soft pancreatic parenchyma (p=0.039), higher postoperative serum amylase (p=0.031), lower postoperative serum albumin (p=0.015) and higher postoperative serum CRP (p=0.004) were significant predictors for development of postoperative PF. In multivariate analysis, male gender (p=0.032), lower postoperative serum albumin (p=0.024) and elevated postoperative serum CRP (p=0.025) were found to be independent risk predictors for postoperative PF.

Table I. *Indication for pancreatic resection and postoperative pancreatic fistula*.

	No. of patients (%)	No. of patients with POPF (%)
Total	297	64 (22%)
Malignant diseases	243 (82%)	51 (21%)
Pancreatic cancer	125 (42%)	21 (17%)
Bile duct cancer	46 (15%)	13 (28%)
Amupulla of Vater cancer	40 (13%)	11 (28%)
Neuroendocrine carcinoma	17 (6%)	2 (12%)
Duodenal adenocarcinoma	7 (2%)	0 (0%)
Other	8 (3%)	4 (50%)
Benign diseases	54 (18%)	13 (24%)
Chronic pancreatitis	9 (3%)	4 (44%)
Mucinous or serous cystadenoma	17 (6%)	3 (18%)
Intraductal papillary mucinous adenoma	14 (5%)	3 (21%)
Other	14 (5%)	3 (21%)

Prediction of PF after pancreatic resection using postoperative albumin and CRP levels. To determine the cut-off for postoperative serum albumin and CRP levels for incidence of postoperative PF, a ROC curve analysis was used (Figure 1A and B). The areas under the curve were 0.621 and 0.644 respectively (p=0.015, p=0.004, respectively) among patients of the early period after pancreatic resection. Therefore, postoperative serum albumin and CRP seem to be valuable prognostic factors predicting for postoperative PF. The closest intersection point to the upper left corner of the ROC curve and the 45-degree line crossing from the upper right to the lower left corner is shown in Figure 1A and B. At the point of intersection, the sensitivity and the specificity of serum albumin and CRP were 0.669 and 0.548, and 0.643 and 0.596, respectively. The levels of postoperative serum albumin and CRP at this point were equivalent to 2.65 g/dl and 9.355 mg/dl respectively, which were judged as appropriate cut-off levels for the prediction of PF after

Table II. *Univariate analysis of postoperative pancreatic fistula after pancreatic resection among patients in the early period (between January 2001 and December 2009).*

Factor	POPF (n=208)		Univariate *p*-value
	Yes (n=42)	No (n=166)	
Age (years)	62.0±13.1*	62.8±12.4	0.679
Gender (male:female)	32:10	94:72	0.020
Postoperative hospital stay (days)	47.9±56.1	27.7±36.1	<0.001
Type of disease (malignant:benign)	32:10	132:34	0.637
Preoperative biliary drainage (yes:no)	9:33	68:98	0.019
Type of resection (PD:non-PD)	25:17	126:40	0.033
Operation time (min)	477.1±163.4	474.9±226.7	0.668
Intraoperative blood loss (ml)	1,362.5±2,016.2	1,363.4±3,109.3	0.811
Perioperative RCC and FFP transfusion (yes:no)	17:25	64:102	0.819
Concominant resection (yes:no)	7:35	31:135	0.764
Cardiovascular diseases (yes:no)	4:38	17:149	0.890
Arterial hypertension (yes:no)	16:26	52:114	0.403
Diabetes mellitus (yes:no)	11:31	36:130	0.533
Body-mass index (≥25:<25 kg/m^2)	6:36	36:131	0.322
Texture of pancreatic parenchyma (hard:soft)	4:38	40:126	0.039
Preoperative lymphocyte count (/μl)	1,591.9±688.9	1,607.8±637.6	0.465
Preoperative serum amylase (IU/l)	107.0±91.4	119.4±137.9	0.480
Preoperative serum albumin (g/dl)	4.01±0.44	3.94±0.43	0.290
Preoperative serum CRP (mg/dl)	0.92±2.38	0.68±2.11	0.907
Postoperative lymphocyte count (/μl)	900.0±376.1	881.9±431.4	0.390
Postoperative serum amylase (IU/l)†	519.3±738.9	386.8±525.4	0.031
Postoperative serum albumin (g/dl)†	2.69±0.46	2.91±0.53	0.015
Postoperative serum CRP (mg/dl)†	10.7±3.84	8.91±3.87	0.004

PD, Pancreaticoduodenectomy; *RCC*, red blood cell concentrate; *FFP*, fresh-frozen plasma; *CRP* C-reactive protein; *Mean±SD, †Values on postoperative day 1.

Table III. *Multivariate analysis of postoperative pancreatic fistula after pancreatic resection among patients in the early period (between January 2001 and December 2009).*

Factor		Multivariate		
		Odds ratio	*p*-Value	95% Confidence interval
Gender	Male	2.503	0.032	1.081-5.796
Postoperative hospital stay (days)		1.008	0.256	0.995-1.021
Preoperative biliary drainage	No	2.228	0.099	0.861-5.766
Type of resection	PD	0.743	0.511	0.306-1.802
Texture of pancreatic parenchyma	Soft	1.938	0.266	0.604-6.224
Postoperative serum amylase (IU/l)†		1.000	0.510	1.000-1.001
Postoperative serum albumin (g/dl)†		0.402	0.024	0.183-0.885
Postoperative serum CRP (mg/dl)†		1.117	0.025	1.014-1.231

PD, Pancreaticoduodenectomy; *CRP* C-reactive protein; †Values on postoperative day 1.

pancreatic resection. For the assessment of postoperative inflammatory response, patients who underwent pancreatic resection in the late period were stratified into three groups: those with high postoperative serum albumin (≥2.7 g/dl) and low postoperative serum CRP (≤10.0 mg/dl) as PIS 0 (n=49), those with low postoperative serum albumin (<2.7 g/dl) or elevated postoperative serum CRP (>10.0 mg/dl) as PIS 1 (n=35), and both low postoperative serum albumin (<2.7 g/dl) and elevated postoperative serum CRP (>10.0 mg/dl) as PIS 2 (n=5).

Table IV. *Univariate analysis of postoperative pancreatic fistula after pancreatic resection among patients in the late period (between January 2010 and December 2011).*

Factor	Postoperative pancreatic fistula (n=89)		Univariate *p*-value
	Yes (n=22)	No (n=67)	
Age (years)	63.5±14.2*	65.8±12.5	0.508
Gender (male:female)	17:5	38:29	0.085
Postoperaive hospital stay (days)	36.5±14.1	22.8±15.9	>0.001
Type of disease (malignant:benign)	19:3	58:9	0.981
Preoperative biliary drainage (yes:no)	9:13	21:46	0.410
Type of resection (PD:non-PD)	15:7	47:20	0.862
Operation time (min)	511.9±122.1	480.0±148.7	0.413
Intraoperative blood loss (ml)	1,101.4±1,028.9	847.5±890.1	0.074
Perioperative RCC and FFP transfusion (yes:no)	7:15	12:55	0.167
Concominant resection (yes:no)	4:18	16:51	0.578
Cardiovascular diseases (yes:no)	3:19	9:56	0.980
Arterial hypertension (yes:no)	12:10	21:44	0.063
Diabetes mellitus (yes:no)	8:14	11:54	0.056
Body-mass index (≥25:<25 kg/m^2)	7:15	7:60	0.017
Texture of pancreatic parenchyma (hard:soft)	3:19	25:42	0.038
Preoperative lymphocyte count (/μl)	1,631.8±460.2	1,371.6±570.7	0.011
Preoperative serum amylase (IU/l)	125.9±110.4	130.0±189.2	0.700
Preoperative serum albumin (g/dl)	3.70±0.40	3.76±0.49	0.580
Preoperative serum CRP (mg/dl)	1.25±3.04	0.42±0.83	0.057
Postoperative lymphocyte count (/μl)†	877.3±311.6	735.7±356.0	0.048
Postoperative serum amylase (IU/l)†	522.0±572.1	396.7±402.3	0.155
PIS (0:1:2)	4:15:3	45:20:2	>0.001

RCC, Red blood cell concentrate; *FFP* fresh frozen plasma; *CRP* C-reactive protein; *PIS* Postoperative Inflammatory Score, *Mean±SD, †Values on postoperative day 1.

Table V. *Multivariate analysis of postoperative pancreatic fistula after pancreatic resection among patients in the late period (between January 2010 and December 2011).*

Factor		Multivariate		
		Odds ratio	*p*-Value	95% Confidence interval
Postoperaive hospital stay (days)		1.054	0.009	1.013-1.096
Body-mass index	≥25	1.788	0.486	0.349-9.158
Texture of pancreatic parenchyma	Soft	2.548	0.230	0.553-11.730
Preoperative lymphocyte count (/μl)		1.001	0.284	0.999-1.002
PIS (0:1:2)	Score 1	7.603	0.005	1.845-31.332
	Score 2	18.454	0.017	1.694-201.061

PIS, Postoperative inflammatory score; †Values on postoperative day 1.

Assessment of PIS in relation to postoperative PF in late period patients. The associations between postoperative PF and perioperative factors including PIS in late-rate period patients are outlined in Table IV and Table V. In univariate analysis, significant risk predictors for postoperative PF consisted of extended postoperative hospital stay (p>0.001), BMI ≥25 (p=0.017), soft pancreatic parenchyma (p=0.038), lower preoperative lymphocyte count (p=0.011) and PIS (p<0.001). In multivariate analysis, extended postoperative hospital stay (p=0.009) and PIS (1: p=0.005, or 2: p=0.017) were found to be independent predictors of PF after resection.

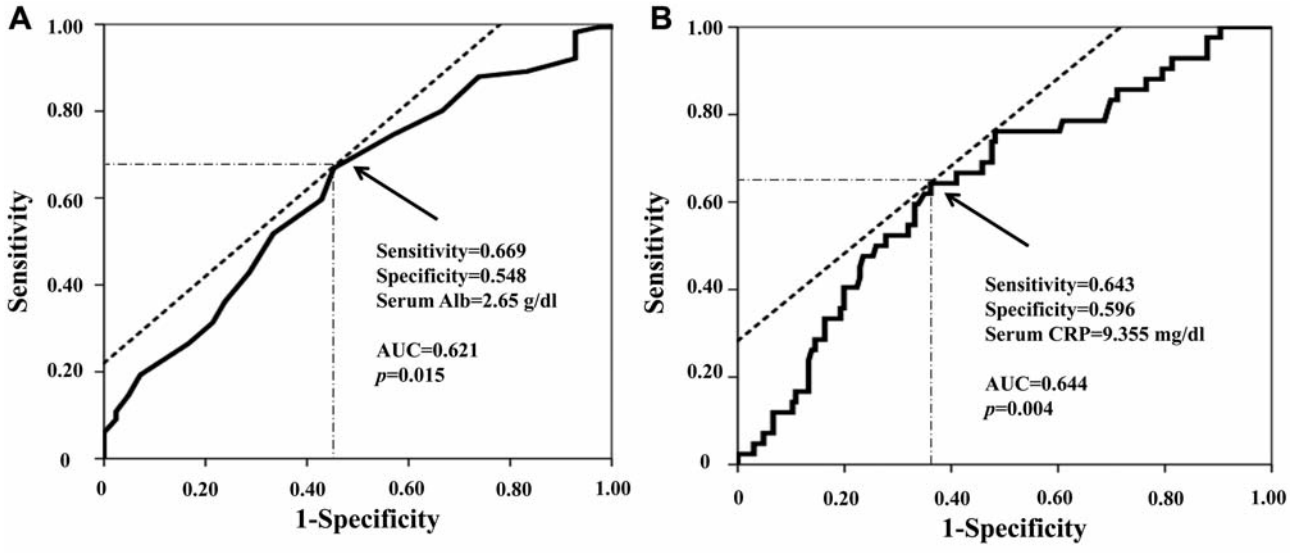

Figure 1. *ROC curves for postoperative serum albumin (A) and serum CRP (B) as predictors of PF.*

Discussion

Recently, several investigators have reported the relation between preoperative systemic inflammation and postoperative complications in patients with various malignant tumors. The Glasgow prognostic score (GPS), calculated using preoperative serum albumin and CRP is a formula to predict cancer-specific prognosis and postoperative complications (10, 11, 15, 16). However, preoperative inflammation by GPS does not reflect the invasiveness of surgical procedures. Few studies have investigated on the relation between postoperative findings and complications with major abdominal surgery. Welsch *et al*. reported that persistence of CRP elevation above 14 mg/dl on postoperative day 4 is predictive of inflammatory postoperative complications including POPF in patients after pancreatic resection (13). Moreover, Wullstein *et al*. reported that peak serum CRP within 72 h after simultaneous pancreas-kidney transplantation predicts graft survival (17). After pediatric kidney and liver transplantation, increased serum CRP was a sensitive marker of rejection episodes, and of bacterial as well as viral infections (18).

Serum albumin is one of the most popular indicators of nutritional status. Hypo-albuminemia is associated with poor tissue healing, reduced collagen synthesis in surgical wounds or at anastomoses, and impairment of immune response, such as macrophage activation and granuloma formation (19, 20). Therefore, wound infection, remote infections such as pneumonia, and anastomotic leakage are commonly observed in hypo-albuminemic patients.

PF is the most relevant major complication of pancreatic resection, and is associated with substantially increased hospital stay and economic resource utilization. Successful management of PF often depends on its early identification, and on this regard, the evaluation of drainage fluid plays a cardinal role (14, 21). However, several investigators have suggested that omission of drainage in elective abdominal surgery is not associated with excessive morbidity. Furthermore, drain placement may increase the rate of infection (22, 23). Conlon *et al*. reported that the use of drains after pancreatic resections did not reduce postoperative complications and patients with drain infection were more likely to develop intra-abdominal abscesses, fluid collections or fistulas (21). Several investigators showed that a prolonged period of drain insertion in patients with low risk of PF was associated with a significantly higher rate of postoperative morbidity and lead to longer hospital stay with increased costs (7, 23). These results suggest that drainage are not mandatory and that if placed, should be removed as soon as possible.

The results of this study show that postoperative systemic inflammatory response, as evidenced by lower serum albumin and elevated CRP on postoperative day 1, was independently associated with an increased risk of the development of PF in patients after elective pancreatic resection. Moreover, risk stratification of patients using the PIS is very convenient because it is includes serum albumin and CRP values on postoperative day 1 which are routinely examined in postoperative patient management.

Conclusion

The PIS on postoperative day 1 is useful for identification of patients who are likely to develop PF after pancreatic resection.

Conflicts of Interest

All Authors declare no conflicts of interests.

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