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C-Reactive Protein Was an Early Predictor of Postoperative Infectious Complications After Pancreaticoduodenectomy for Pancreatic Cancer

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Objective: The study objective was to assess the predictive value of C-reactive protein (CRP) for the early detection of postoperative infectious complications (PICs) after pancreaticoduodenectomy.

Summary of Background Data: The incidence of PICs after pancreaticoduodenectomy still remains high and a clinically relevant problem, despite improvements in the surgical procedure.

Methods: We examined 110 consecutive patients who underwent pancreaticoduodenectomy for primary pancreatic cancer between 2006 and 2014. The predictive value was assessed by estimating the area under the receiver operating characteristic curve (AUC). Clinical and laboratory data, including CRP, were analyzed with univariate and multivariate logistic regression analyses to identify predictors of PICs of grade III or higher according to the Clavien-Dindo classification.

Results: PICs of grade III or higher occurred in 13 patients [11.8%; 95% confidence interval (CI), 6.45%–19.36%]. CRP level on postoperative day 3 (POD 3) was a good predictor of

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PICs (AUC, 0.815; 95% CI, 0.651–0.980), showing the highest accuracy among clinical and laboratory data. A cutoff value of 13.2 mg/dL yielded a sensitivity of 0.846 and a specificity of 0.794. On multivariate analysis, a POD 3 CRP level of 13.2 mg/dL or higher (odds ratio, 20.0; 95% CI, 4.07–97.9; $P = 0.002$) was a significant predictor of PICs after pancreaticoduodenectomy.

Conclusions: CRP elevation above 13.2 mg/dL on POD 3 is a significant predictive factor for PICs and should prompt an intense clinical search and therapeutic approach for PICs.

Key words: Pancreaticoduodenectomy – CRP – Infectious complications

Pancreatic cancer is a major cause of cancer death worldwide, with a 5-year survival rate of less than 5%.[1] Pancreaticoduodenectomy (PD) is essential for the cure of pancreatic head cancer.[2–4] However, the postoperative infectious complication (PIC) rate after PD has been reported to range from 30% to 65%.[5,6]

Recent studies have demonstrated that the development of PICs decreased patient survival or increased the risk of disease recurrence in various types of malignancies. For instance, Aoyama *et al*[7] examined 164 patients who underwent curative surgery for pancreatic cancer and classified patients into those with and those without PICs. They found that PICs were a risk factor for pancreatic cancer survival and recurrence.[7] Moreover, some authors have suggested that the immunologic response against PICs enhanced the viability of undetectable residual tumor cells after surgery, thereby increasing disease recurrence.[8–10]

C-reactive protein (CRP) is an acute-phase protein, and its short half-life of 19 hours makes it a valuable marker to detect disease activity, inflammatory response, and postoperative recovery.[11] Measuring CRP levels is widely available and well established in routine clinical practice because of its low cost, unlike procalcitonin[12,13] or interleukin 16,[14,15] other recently described markers of systemic inflammation. The predictive value of postoperative CRP levels to rule out infectious complications after colorectal, gastroesophageal, and pancreatic surgery has been previously assessed, and some of the studies showed a high level of accuracy.[6,16–24] However, few studies enrolled only patients who underwent PD for pancreatic head cancer.

The aim of the present study was to investigate predictive clinical factors, including CRP, for the early detection of PICs in consecutive patients who had undergone PD for pancreatic head cancer.

Patients and Methods

Patients

The patients were selected from the medical records of 110 consecutive patients who underwent PD for pancreatic cancer at Kanagawa Cancer Center from October 10, 2006, to December 22, 2014, according to the following criteria: (1) a pathologically common type of pancreatic cancer according to the International Union Against Cancer (UICC) TNM 7th edition[25]; and (2) those who had undergone a gross complete (R0 or R1) resection of pancreatic cancer as initial treatment. The resected specimens were examined histopathologically and staged according to the UICC TNM 7th edition. Patients with other pancreatic and periampullary neoplasms, such as intraductal papillary mucinous neoplasms, cystadenocarcinoma, and endocrine tumors, were excluded.

This study was approved by the Institutional Review Board of the Kanagawa Cancer Center (IRB no. 22epidemiology38). Written informed consent was obtained from all participants prior to surgery.

Surgical procedure

All patients underwent subtotal stomach-preserving PD[26] as the standard procedure. Lymph node groups resected en bloc included the anterior pancreatic duodenal lymph nodes, the posterior pancreatic duodenal lymph nodes, nodes in the lower hepatoduodenal ligament, and nodes along the right lateral aspect of the superior mesenteric artery and vein. In our institution, we cut the pancreas using an energy device. The modified Child method[27] of reconstruction, which included end-to-side pancreaticojejunostomy and duct-to-mucosa anastomosis with a 5-Fr lost stent tube, was performed with eight 5-0 monofilament absorbable sutures, and approximation of the pancreas stump and jejunal wall using four 3-0

monofilament absorbable interrupted sutures was performed.[28] End-to-side hepaticojejunostomy was performed without a stent. Anastomosis between the jejunum and the stomach with antecolic reconstruction was made. Multiple intraperitoneal drains were placed: the first was placed posterior to hepaticojejunostomy, the second was placed in the foramen of Winslow, and the third was placed on the anterior surface of the pancreaticojejunostomy. To prevent hypothermia, a blanket warming system and warming set for intravenous infusion were used.

Perioperative care

In principle, the patients all received the same perioperative care. In brief, the patients were allowed to eat until midnight on the day before the surgery and were required to drink the contents of two 500-mL plastic bottles containing oral rehydration solution until 3 hours before surgery. The nasogastric tube was removed on postoperative day 1 (POD 1) after surgery. Oral intake was initiated on POD 2, beginning with water and an oral nutritional supplement. The patients began to eat solid food on POD 5, starting with rice gruel and soft food and advancing in 3 steps to regular food intake. The patients were discharged when they achieved adequate pain relief and soft food intake, returned to their preoperative mobility level, and exhibited normal laboratory data.

Definition of surgical complications

Complications of grades III to V according to the Clavien-Dindo classification[29,30] that occurred during hospitalization and/or within 30 days after surgery were retrospectively determined from the patient's record. A pancreatic fistula was defined according to the international study group on pancreatic fistula (ISGPF) criteria.[31,32] Delayed gastric emptying was defined as a nasogastric tube that remained *in situ* or was reinserted after POD 3 (ISGPS definition).[33] PICs were defined as follows: postoperative pancreatic fistulas (POPFs), leakage of the gastrojejunal or choledochojejunal anastomosis, intraabdominal abscesses, cholangitis, pneumonia, or urinary tract infections. Grades I to II complications were not evaluated in order to exclude the possibility of a description bias in the patient's records. The serum levels of CRP were measured on PODs 1, 3, 5, and 7.

Table 1 Clinicopathologic features of 110 patients

	Value
Patients, N	110
Age, y, median (range)	68 (40–83)
Sex, n (%)	
Male	59 (53.6)
Female	51 (46.4)
BMI, kg/m^2, median (range)	21.71 (15.7–33.73)
Preoperative serum Alb level, g/dL, median (range)	4.0 (3.0–5.0)
ASA-PS, n (%)	
1	14 (12.7)
2	93 (84.5)
3	3 (2.7)
Clinical stage, n (%)	
IA	3 (2.7)
IB	28 (25.5)
IIA	39 (35.5)
IIB	34 (30.9)
III	6 (5.5)
Operative time, min, median (range)	517.5 (198–840)
Blood loss, mL, median (range)	1015 (265–6730)
PICs according to the Clavien-Dindo classification, n (%)	
None, or grade II or lower	97 (88.2)
Grade III or higher	13 (11.8)

Statistical analysis

All statistics analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[34] A two-sided P value <0.05 was considered to be significant. Continuous data are presented as the mean ± SD or median with range. The Mann-Whitney test and Fisher exact test were employed to evaluate differences in continuous and categoric variables, respectively. Diagnostic accuracy was determined by the area under the receiver operating characteristic curve (AUC).[35–37] The optimal cutoff values were determined by maximizing Youden index (sensitivity + specificity − 1). Univariate and multivariate logistic regression analyses were used to identify the clinical risk factors for PICs of grade III or higher according to the Clavien-Dindo classification.

Results

Patient characteristics

The patient characteristics are shown in Table 1. The median age of patients was 68 years (range, 64–73

Table 2 Details of PICs

	Clavien-Dindo classification, n					Total, n (%)
	Grade IIIa	Grade IIIb	Grade IVa	Grade IVb	Grade V	
POPF	6	2	0	1	0	9 (8.2)
Intra-abdominal abscesses	2	0	0	0	0	2 (1.8)
Cholangitis	0	0	0	1	0	1 (0.9)
Leakage of the choledochojejunal anastomosis	1	0	0	0	0	1 (0.9)
Leakage of the gastrojejunal anastomosis	0	0	0	0	0	0 (0)
Pneumonia	0	0	0	0	0	0 (0)
Urinary tract infections	0	0	0	0	0	0 (0)
Surgical site infections	0	0	0	0	0	0 (0)

years), and 51 of 110 patients (46%) were women. The mean body mass index (BMI) and preoperative serum albumin (Alb) level of all patients were 21.7 kg/m^2 (range, 15.7–33.7 kg/m^2) and 4.0 g/dL (range, 3.0–5.0 g/dL), respectively. A total of 107 patients had an American Society of Anesthesiologists Physical Status (ASA-PS) of 1 or 2. The median operative time and the median blood loss were 517.5 minutes (range, 198–840 minutes) and 1015 mL (range, 265–6730 mL), respectively.

Surgical morbidity and mortality

PICs of grade III or higher according to the Clavien-Dindo classification occurred in 13 patients (11.8%). Pancreatic fistula was observed in 8 and abdominal abscess in 2, and no patients died during hospitalization. The details of the complications are shown in Table 2. POPF was the most frequently diagnosed complication, followed by intraabdominal abscess and cholangitis.

Associations between postoperative CRP level and PICs

CRP level peaked on POD 3 in patients with PICs of grade III or higher, at which point the CRP level was significantly higher than that in patients with PICs of grade II or lower. The CRP values from POD 3 through POD 7 were 17.63 ± 8.18 mg/dL on POD 3, 10.55 ± 6.16 mg/dL on POD 5, and 9.56 ± 6.81 mg/dL on POD 7 in patients with PICs of grade III or higher; and 8.91 ± 5.01 mg/dL on POD 3, 4.07 ± 4.44 mg/dL on POD 5, and 3.04 ± 3.35 mg/dL on POD 7 in patients with PICs of grade II or lower. A significant difference in the CRP level on POD 5 ($P < 0.0001$) and POD 7 ($P < 0.0001$) was observed between patients with and without PICs of grade III or higher.

Receiver-operating characteristic analysis evaluated the diagnostic accuracy of CRP level on POD 3 for the occurrence of PICs of grade III or higher, as shown in Fig. 1. The CRP level on POD 3 showed a superior diagnostic accuracy [AUC, 0.817; 95% confidence interval (CI), 0.651–0.980], with an optimal cutoff value of 13.2 mg/dL. The sensitivity was 84.6%, and the specificity was 79.4% when a CRP level of 13.2 mg/dL was set as the cutoff value.

Risk factors for PICs

The results of univariate and multivariate analyses of various clinical factors, such as age, sex, preoperative BMI, Alb level, ASA-PS, operative time, intraoperative blood loss, and POD 3 CRP level for PICs of grade III or higher are shown in Table 2. We used the medians as the cutoff points for BMI, Alb, operative time, and intraoperative blood loss. Multivariate analyses found that only a CRP level on POD 3 of 13.2 mg/dL or higher (odds ratio, 18.5; 95% CI, 2.88–119) was a significant independent predictive factor for PICs after PD among these factors (Table 3). Patients with a CRP level higher than 13.2 mg/dL on POD 3 had a significantly higher POPF (grade III or above) rate than those with lower CRP levels ($P < 0.001$).

Discussion

The present study found that CRP level on POD 3 had a superior diagnostic accuracy for PICs, and the optimal cutoff value for CRP was determined to be 13.2 mg/dL. Moreover, the univariate and multivariate analyses identified CRP level ≥13.2 mg/dL on POD 3 as a significant independent predictive factor for PICs after PD. Therefore, the CRP measurement on POD 3 may be a useful and relevant marker for clinical assessment after PD.

Similar results were observed in previous reports. Warschkow *et al*[16] assessed the diagnostic accuracy of the CRP level for the occurrence of PICs in 280

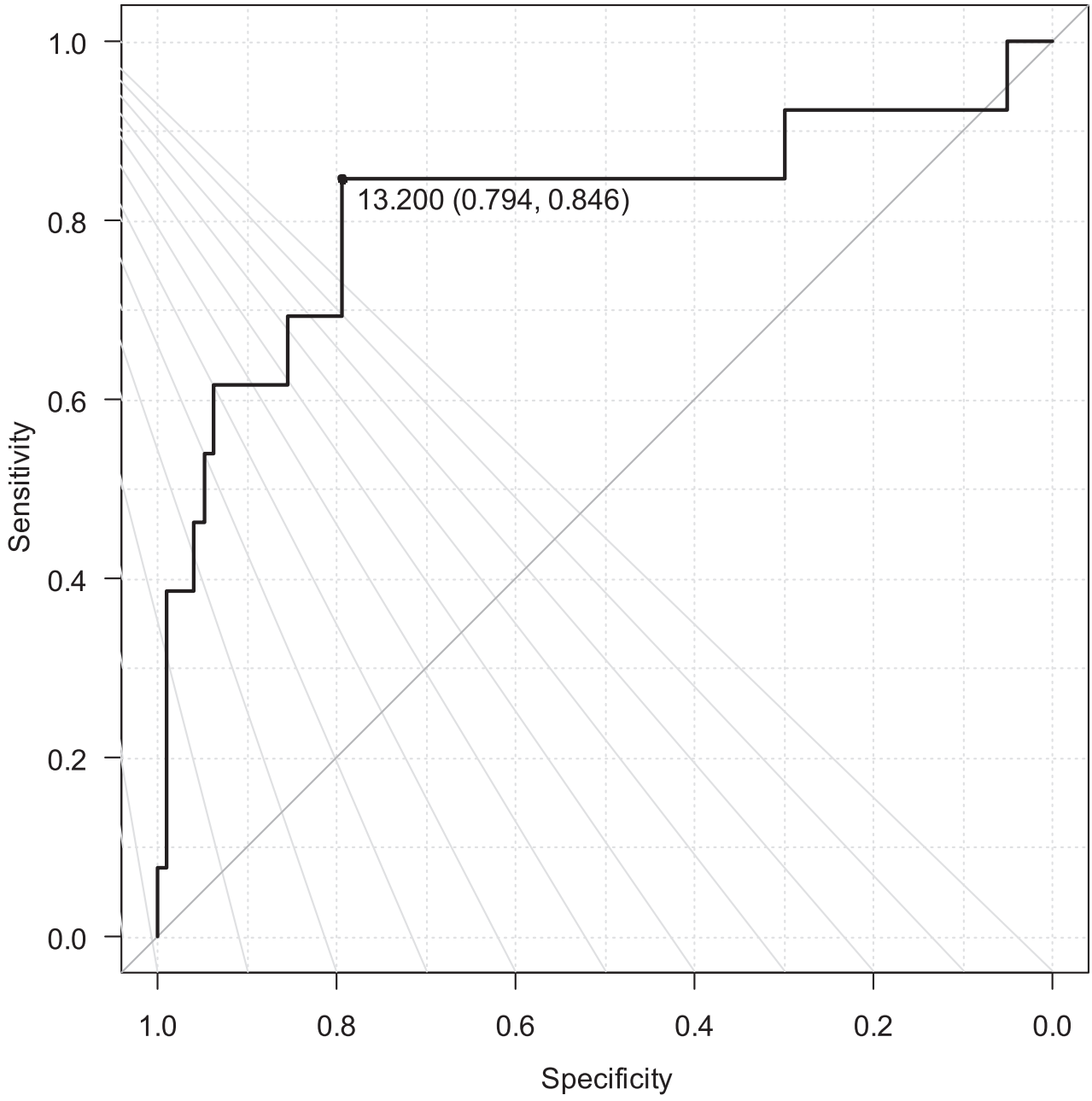

Fig. 1 Association between postoperative CRP level and PICs.

patients after pancreatic surgery. They reported that the diagnostic sensitivity on POD 4 was 63% (95% CI, 50%–76%), and the specificity was 79% (95% CI, 71%–88%) using a cutoff CRP value of 18.4 mg/dL. In this study, they found that CRP levels had a moderate diagnostic accuracy for PICs after pancreatic surgery. In addition, Welsch *et al*[6] also reported a moderate accuracy of CRP for PICs. They evaluated 688 patients undergoing pancreatic resections with pancreaticojejunostomy. They reported that a cutoff CRP value of 14.0 mg/dL on POD 4 yielded a sensitivity of 69.5% and a specificity of 87.1% for PICs. These findings suggested that persistent elevation of CRP after pancreatic resection can indicate the development of inflammatory complications.

In the present study, diagnostic accuracy was determined by the AUC.[35–37] The optimal cutoff

Table 3 Predictive factors for PICs of grade III or higher

Patient characteristics	No. of patients	Patients with PICs of grade III or higher, n (%)	Univariate analysis			Multivariate analysis		
			Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age								
≥75 y	23	2 (8.7)	1	0.29–15.12	1	1	0.23–20.00	0.50
<75 y	87	11 (12.6)	1.51			2.15		
Sex								
Female	51	3 (5.9)	1	0.77–19.39	0.084	1	0.50–17.90	0.23
Male	59	10 (16.9)	3.23			2.99		
BMI								
<22 kg/m^2	58	3 (5.2)	1	1.02–25.88	0.004	1	0.29–8.16	0.61
≥22 kg/m^2	52	10 (19.2)	4.31			1.54		
Preoperative serum Alb level, g/dL								
<4.0 g/dL	50	3 (6.0)	1	0.89–22.8	0.072	1	0.56–16.10	0.20
≥4.0 g/dL	51	10 (19.6)	3.77			3.01		
ASA-PS								
1 or 2	107	12 (11.2)	1	0.062–79.81	0.32	1	0.35–139	0.20
3	3	1 (33.3)	3.88			6.98		
Clinical stage								
IA/IB	31	3 (9.7)	1	0.31–8.19	1	1	0.31–14.29	0.45
IIA/IIB/III	79	10 (12.7)	1.35			2.08		
Operative time								
<520 min	57	6 (10.5)	1	0.34–5.02	0.77	1	0.33–11.11	0.47
≥520 min	53	7 (13.2)	1.29			1.92		
Blood loss								
<1000 mL	53	5 (9.4)	1	0.42–6.52	0.56	1	0.29–9.03	0.58
≥1000 mL	57	8 (14.0)	1.56			1.63		
CRP level on POD 3								
<13.2 mg/dL	79	2 (2.5)	1	4.00–203.68	<0.001	1	3.05–147	0.002
≥13.2 mg/dL	31	11 (35.5)	20.42			21.2		

values were determined by maximizing Youden index (sensitivity + specificity − 1). The estimated optimal cutoff value of 13.2 mg/dL for CRP on POD 3 yielded a positive predictive value of 35.5% (95% CI, 19.2%–54.6%) and a negative predictive value of 97.5% (95% CI, 91.2%–99.7%). The high negative predictive value of 97.5% suggested that the development of PICs can be ruled out when the CRP value on POD 3 is 13.2 mg/dL or lower, whereas the positive predictive value of 35.5% is too low to rule in PICs. The predictive value of postoperative CRP levels to rule out infectious complications after colorectal, gastroesophageal, and pancreatic surgery has been assessed previously, and some studies showed a high level of accuracy,[6,16,17,22,23,38–42] as shown in Table 4. The receiver operating characteristic analysis indicated that not identical, but similar CRP levels provided the optimal cutoff value to balance the sensitivity and specificity in various gastrointestinal cancer surgeries.

There are several possible reasons why CRP affected the PIC of pancreatic cancer patients. One possible reason for this association was that lipopolysaccharide release due to bacterial infection and tissue ischemia induced the release of interleukin 6 (and other cytokines), which was the chief stimulator of hepatocellular CRP synthesis. This mechanism was also associated with a higher POPF (grade III or higher) rate in patients with CRP levels above 13.2 mg/dL on POD 3. However, the precise mechanism remains unknown.

Previously, clinicopathologic factors, such as white blood cells (WBCs), procalcitonin, and interleukin 6, were reported to be significant risk factors that could be used to predict PICs after PD. For instance, WBC count has been reported to have a poor diagnostic accuracy for detecting PICs, because the counts do not differ significantly from uneventful courses until later stages. Warschkow *et al*[18] evaluated 1187 patients who underwent colorectal cancer surgery and assessed the diagnostic accuracy of the WBC count on POD 3 using a receiver operating characteristic analysis. They reported that a cutoff WBC count of 9900/μL on POD 3 yielded a sensitivity of 41% (95% CI, 34%–49%) and a

Table 4 Literature examining the value of CRP level for predicting PICs following gastrointestinal cancer surgery

Source, y	Type of cancer	Patients, n	POD	CRP cutoff, mg/dL	Sensitivity, %	Specificity, %	AUC
Welsch *et al*,[38] 2007	R	48	3	14.0	80	81	0.88
Korner *et al*,[41] 2009	CR	231	3	19.0	82	73	0.82
MacKay *et al*,[40] 2011	CR	160	4	14.5	85	86	0.87
Warschkow *et al*,[23] 2012	CR	1187	4	12.3	66	77	0.76
Platt *et al*,[39] 2012	CR	454	3	17.0	74	75	0.80
Dutta *et al*,[42] 2011	EG	136	3	18.0	52	64	0.81
Warschkow *et al*,[17] 2012	EG	210	4	14.1	78	70	0.77
Shishido *et al*,[22] 2016	G	417	3	17.7	66	84	0.80
Welsch *et al*,[6] 2008	P	688	4	14.0	70	87	0.86
Warschkow *et al*,[16] 2012	P	280	4	18.4	50	76	0.67
Present study	P	110	3	13.2	84.6	79.4	0.82

CR, colorectal; EG, esophagogastric; G, gastric; P, pancreatic; R, rectal.

specificity of 79% (95% CI, 73%–83%) for PICs. That study suggested that the diagnostic accuracy of the WBC count was lower than that of CRP level in the present study. Procalcitonin has also been described as a promising marker to predict PICs after abdominal surgery; however, the use of this marker is controversial and associated with high costs.[15,43] Silvestre *et al*[19] evaluated 50 patients who underwent colorectal surgery with primary anastomosis in a prospective, observational study. They evaluated both CRP and procalcitonin. They reported that procalcitonin had a lower AUC than CRP. Furthermore, unlike CRP, measurement of procalcitonin level is not widely available or well established in routine clinical practice.

There are some limitations associated with this study. First, this was a retrospective, single-center study. We cannot deny the possibility that our findings were observed by chance, and the true cutoff CRP value is unknown. Second, we evaluated PICs according to the Clavien-Dindo classification, which is different from previous studies. Considering these limitations, further studies should investigate whether early diagnostic or therapeutic approaches based on an elevated CRP level on POD 3 actually lead to earlier detection of PICs, improved outcomes, and reduced morbidity after PD.

In conclusion, this study found that measurement of the CRP on POD3 had a superior diagnostic accuracy for PICs. The cutoff value for CRP was determined to be 13.2 mg/dL and was identified as a significant independent predictive factor for PICs after PD. Our findings might help physicians predict a patient's postoperative course and facilitate decision-making regarding prompt, comprehensive clinical evaluations for PICs.

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