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Prognostic Impact of Pre- and Post-operative P-CRP Levels in Pancreatic Cancer Patients

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ABSTRACT

Background C-reactive protein (CRP) levels reflect ongoing inflammation and/or tissue damage, and studies suggest that platelets play a role in tumor invasion and metastasis. P-CRP is defined as the multiplied product of serum CRP and platelet levels. Here the prognostic value of pre- and post-operative P-CRP levels in pancreatic cancer (PC) patients was assessed.

Methods This retrospective study used data from 107 consecutive PC patients who had undergone either pancreaticoduodenectomy or distal pancreatectomy. Clinicopathological parameters and pre/post-operative laboratory data derived from patient records were used for analyses. P-CRP was defined as the product of peripheral thrombocyte count (/uL) × serum CRP level (mg/dL) divided by 10^4; the optimal P-CRP cut-off value was defined using receiver operating characteristic curves.

Results PC patients were classified as either P-CRP^{Low} (< 1.782; n = 49) or P-CRP^{High} (≥ 1.782; n = 58), based on the cut-off value of 1.782. Univariate analysis revealed that performance status, clinical stage, pathological T and N stages, P-CRP, and carbohydrate antigen 19-9 (CA19-9) significantly affected overall survival (OS). Multivariate analysis revealed that independent risk factors for OS were pathological N stage, P-CRP, and CA19-9. Additionally, 103 PC patients for whom postoperative data were available were classified into four groups (P-CRP$^{Low\text{-}Down}$, P-CRP$^{Low\text{-}Up}$, P-CRP$^{High\text{-}Down}$ and P-CRP$^{High\text{-}Up}$), based on preoperative P-CRP and postoperative trend of P-CRP, and we found that prognosis, in terms of OS, was significantly different among these groups (P = 0.012).

Conclusion Pre- and post-operative P-CRP values are a potential predictor of prognosis in PC patients.

Key words CRP; pancreatic cancer; platelet; prognosis

Despite advances in the treatment and care for pancreatic cancer (PC), prognosis remains poor as 5-year survival is less than 10%,[1] and multidisciplinary strategies for diagnosis and treatment have been evaluated to improve outcomes.[2, 3] The relationship between tumorigenesis and inflammation has been known ever since Rudolf Virchow first reported the presence of leukocytes within tumors in the 19th century,[4] while the underlying molecular mechanisms continue to be elucidated.[5] Consistent with this, it is known that PC development requires a certain type of inflammation in the microenvironment,[6] e.g. pancreatic satellite cells,[7–9] and currently, inflammation is known to be an important hallmark of malignancy.

In recent years, several indicators based on common inflammatory factors such as CRP, platelets and leukocytes have been reported to have prognostic value in various human tumors.[10–12] While these indicators have the advantage of simplicity of evaluation, the mechanism (or mechanisms) by which they affect tumorigenesis have not been described in detail. Nonetheless, a potential common mechanism underlying the prognostic impact of these indicators may be an association with systemic and/or local inflammation. Over the past few years, it has been widely known that inflammation caused by several sources plays a critical role in tumorigenesis. For examples in the gastrointestinal field, *Helicobacter pylori* infection leads to chronic gastritis and gastric cancer,[13, 14] and chronic HBV/HCV infection increases the risk of hepatocellular carcinoma.[15] Recently, the molecular pathways and mechanisms by which inflammation induces tumorigenesis have been partially elucidated and they appear to be mediated through proteins such as NF-κB and

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Abbreviations: AC, adjuvant chemotherapy; AUC, area under the curve; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen: CD classification, Clavien-Dindo classification; CRP, C-reactive protein; DP, distal pancreatectomy; ECOG, Eastern Cooperative Oncology Group; EMT, epithelial-to-mesenchymal transition; NAC, neoadjuvant chemotherapy; OS, overall survival; PC, pancreatic cancer; PD, pancreaticoduodenectomy; PS, performance status; PVR, portal vein resection; POPF, postoperative pancreatic fistula; ROC, receiver operating characteristic; UICC, Union for International Cancer Control

STAT3.[16] Particularly, PC development is involved with a certain type of inflammation in the microenvironment of cancer.[6, 8]

CRP is predominantly produced by the liver in response to an inflammatory stimulus that involves increased cytokine expression; and serum CRP value reflects ongoing inflammation and/or tissue damage.[17] Interestingly, while one study has demonstrated that human CRP activation itself is one of the mediators of tissue injury,[18] it is not known if CRP has a direct molecular role in tumor progression.

Platelets (also called thrombocytes), are a component of blood whose function is to initiate blood clot formation. In the process of inflammation, it is known that platelets are exposed to soluble mediators such as lipid mediators, cytokines and chemokines released by activated leucocytes, endothelial cells and perivascular cells.[19] Importantly, platelets are an important source of cytokines that enhance tumor angiogenesis; this concurs with the fact that thrombocytopenic mice are protected against metastasis, which was established as early as 1968.[20] Labelle et al. have reported that platelets co-cultured with breast carcinoma cells induce cancer stemness.[21] They demonstrate further that platelets promote both TGF-β and NFκ-B pathways, inducing an epithelial-to-mesenchymal transition (EMT) in breast and colon carcinoma cell lines, thus, facilitating a metastatic phenotype. In addition to the above, they are known to release multiple factors that play a role in tumor invasion and metastasis.[22] Furthermore, clinical studies have demonstrated that a high platelet count is associated with increased mortality in a variety of cancers, including gynecological malignancies and lung, renal, gastric, colorectal, and breast cancers.[23–30]

Recently, an index calculated using platelet count and C-reactive protein (CRP) levels has been reported as a prognostic factor in PC, and P-CRP value, whose calculation is based on measured values of platelets and CRP [peripheral thrombocyte count (/uL) × serum CRP level (mg/dL) divided by 10^4], has also been reported as a prognostic indicator in gastric cancer.[31]

P-CRP value is a simple multiplied product of the measured values of platelets and CRP. In gastric cancer patients, P-CRP value is a known synergistic prognostic indicator whose importance is emphasized more than that of either CRP or platelet levels alone.[31]

However, as these previous studies had focused on the patient's condition before surgery only, the prognostic potential of postoperative P-CRP and its relationship with preoperative values remains unclear. Thus, this retrospective study investigated the prognostic value of pre- and post-operative P-CRP values in PC patients.

MATERIALS AND METHODS

Patients

Between August 2005 and August 2016, 107 consecutive PC patients underwent pancreatic resection at the Tottori University Hospital (Yonago, Japan) and were included in this retrospective study. All patients underwent either pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) by open laparotomy. Surgeons with substantial hepato-biliary-pancreatic surgical expertise performed all the procedures at the Tottori University Hospital. PC patients were classified by clinical symptom and pathological detection according to 7th edition of the Union for International Cancer Control (UICC) TNM staging system. The study protocol was approved by the ethical review board of Tottori University (approval number: 17A135).

Parameters

The clinicopathological parameters and laboratory data of all patients were extracted from the electronic medical records. These included patient characteristics such as age, gender, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status (PS), tumor location, preoperative biliary infection, neoadjuvant chemotherapy (NAC), UICC stage, histological type, T/N stages, vascular invasion, perineural invasion, and lymphatic vessel invasion and surgical and postoperative parameters such as adjuvant chemotherapy(AC), operation time, blood loss volume, portal vein resection (PVR), R0 resection, postoperative pancreatic fistula (POPF), and postoperative complications.

Postoperative complications that occurred within 30 days were evaluated using the Clavien-Dindo (CD) classification system.[32] POPF was assessed according to consensus guidelines issued by the International Study Group of Pancreatic Fistula.[33]

The P-CRP value was defined as the product of peripheral thrombocyte count (/uL) × serum CRP level (mg/dL) divided by 10^4.The optimal cut-off value was defined based on the receiver operating characteristic (ROC) curve for P-CRP that included data on two-year-survival after either PD or DP.

Follow-up

After the operation, all the patients had regular follow-ups to obtain their survival data by means of retrieving medical records, and communication by mail and telephone. Postoperative P-CRP values were checked with PC patients during their first visits after discharge, which was approximately 1 month later.

Statistical analysis

Continuous variables were reported as means and standard deviations, while categorical data were reported as proportions (%). Univariate analyses were performed using Fisher's exact test for categorical variables, and Mann-Whitney *U*-test for continuous variables. Cox proportional hazard model was used to calculate the hazard ratios for multivariate analysis. All statistical analyses were performed using the statistical software SPSS v. 23.0 statistical software (IBM Corporation, Armonk, NY), and P values less than 0.05 were considered statistically significant.

RESULTS

Table 1 summarizes all patient characteristics. Using preoperative laboratory data, the cut-off value of P-CRP was determined to be 1.782 (area under the curve, AUC = 0.67), and additionally, CRP and platelet values were also analyzed by ROC curves (AUC = 0.66 and 0.51, respectively; Fig. 1). In addition, we analyzed CA19-9, which has been reported to be one of the prognostic markers of pancreatic cancer, by ROC curve (AUC = 0.73). Then, all PC patients were classified into P-CRP^{Low} (< 1.782) group (n = 49) and P-CRP^{High} (≥ 1.782) group (n = 58) according to the cut off value.

Table 2 shows the comparison of clinicopathological factors between the P-CRP^{Low} and P-CRP^{High} groups. Operation time and blood loss had significant differences between P-CRP^{Low} and P-CRP^{High} groups, while other factors including preoperative biliary infection did not significantly differ between the two groups.

Table 3 shows the relationship between clinicopathological factors of PC patients and overall survival (OS), using Kaplan–Meier method and log rank test. Univariate analysis identified PS, UICC stage, pathological T and N stages, P-CRP, and carbohydrate antigen 19-9 (CA19-9) as significant predictors of OS, while other factors such as age, sex, BMI, tumor location, preoperative infection, NAC, AC, PVR, R0 resection, histology, POPF, postoperative complication, and carcinoembryonic antigen (CEA) were not significant.

CA19-9, which is one of the most common tumor markers with regards to prognosis in PC, had no significant correlation with P-CRP (Fig. 2). Multivariate analysis revealed that the independent risk factors for OS were pN stage, P-CRP and CA19-9 (Table 4).

To evaluate the relationship between postoperative changes in P-CRP and prognosis, 103 PC patients whose postoperative data were available were classified into four groups, namely P-CRP$^{Low\text{-}Down}$, P-CRP$^{Low\text{-}Up}$, P-CRP$^{High\text{-}Down}$ and P-CRP$^{High\text{-}Up}$, based on postoperative changes in P-CRP compared to preoperative P-CRP. Next, survival analysis in the four groups, performed using the Kaplan–Meier method, showed that prognosis (as OS) was significantly different among these four groups (Fig. 3, P = 0.012).

DISCUSSION

Here, we have evaluated the prognostic value of P-CRP in patients who had undergone surgery for PC using a preoperative cut-off value of 1.782, determined by ROC analysis, because the AUC value for P-CRP was greater than that of either platelet or CRP (0.67 vs. 0.51, 0.66). This observation implies that the combination of platelet and CRP can better predict the prognosis in PC patients.

CA19-9, which is a substance elevated in many PC patients and one of the most common tumor markers with regards to prognosis in PC (as shown in Fig. 1), had no significant correlation with P-CRP. This result suggests that CA19-9 and P-CRP are independent predictors from each other.

As Table 2 shows, patients in the P-CRP^{High} group underwent significantly longer procedures and experienced greater blood loss compared to those in the P-CRP^{Low} group. P-CRP^{High} group had longer operation time and greater blood loss than P-CRP^{Low} group with statistical significance. These differences may have been caused by endogenous inflammatory conditions of tumor[6] in the P-CRP^{High} group, such as fibrotic changes or greater bleeding tendency, which can make the procedure more difficult. Additionally, the presence of preoperative biliary infection did not differ significantly between the two groups, suggesting that preoperative inflammation might predominantly originate from the tumors themselves. Furthermore, tumor location had no relation to P-CRP as well as OS (Tables 2 and 3).

Univariate analysis revealed that P-CRP^{High} patients had a significantly poorer prognosis than P-CRP^{Low} patients, and multivariate analysis showed that P-CRP was an independent predictor of OS in PC patients. Furthermore, we hypothesized that postoperative P-CRP value may affect the prognosis of PC and analyzed the prognosis of four groups according to preoperative P-CRP and postoperative alteration of the value; P-CRP$^{Low\text{-}Down}$, P-CRP$^{Low\text{-}Up}$, P-CRP$^{High\text{-}Down}$ and P-CRP$^{High\text{-}Up}$.

The Kaplan-Meier method showed differences with statistical significance between four groups. This indicates the postoperative P-CRP may offer further significance of the prognosis in both P-CRP^{High} and P-CRP^{Low} groups. These results suggest that preoperative inflammatory state and levels of prolonged postoperative inflammation can affect cancer malignancy, including metastasis and local recurrence after surgery.

Table 1. Patient characteristics

		n = 107
Age (years)		71.1 ± 8.4
Sex	Male	68
	Female	39
BMI (kg/m^2)		21.8 ± 3.1
PS	0	69
	1	36
	2	2
Tumor location	Head	67
	Body/Tail	40
Preoperative Infection	Yes	13
	No	94
NAC	Yes	13
	No	94
Stage	0	8
	IA	5
	IB	3
	IIA	33
	IIB	56
	III	0
	IV	2
Histology	PDAC	86
	Others (including IPMC)	21
T stage	Tis	8
	T1	5
	T2	5
	T3	89
N stage	N1	58
	N0	49
Vascular invasion	Yes	87
	No	20
Perinural invasion	Yes	90
	No	17
Lympho invasion	Yes	89
	No	18
AC	Yes	54
	No	53
Operation time (h)		7.72 ± 2.48
Blood loss (g)		665 ± 582
PVR	Yes	23
	No	84
R0	Yes	90
	No	17
POPF ≥ grade B	Yes	26
	No	81
Complication CD ≥ 2	Yes	36
	No	71

AC, adjuvant chemotherapy; BMI, body mass index; CD, Clavien-Dindo Classification; NAC, neoadjuvant chemotherapy; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula; PS, performance status; PVR, portal vein resection.

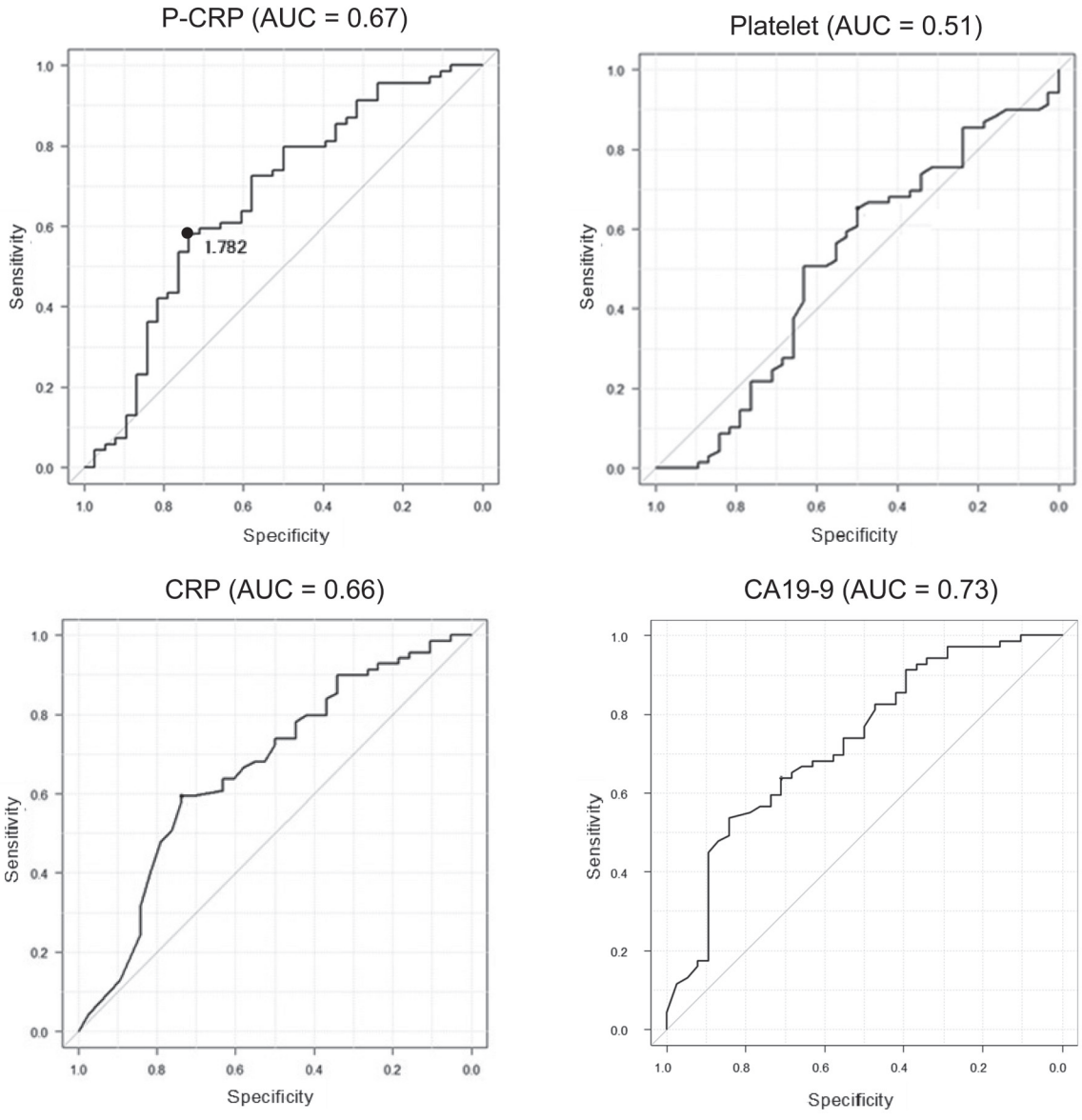

Fig. 1. ROC curves and AUC for P-CRP, platelet, CRP and CA19-9.

This study has a few limitations in that it is a single-institution, retrospective study, with a small sample size. Nevertheless, as there are very few studies that have focused on the relation of both pre/postoperative P-CRP values and prognosis in PC patients, the results presented here may help categorize the patients who undergo surgery into high/low risk–groups with respect to OS.

To summarize, this study revealed that pre- and post-operative inflammation can be strengthened with P-CRP and predict the prognosis in PC patients. Therefore, the role of inflammation-based factors such as P-CRP should be verified by future large-scale clinical studies.

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The authors declare no conflict of interest.

Table 2. Comparison of clinicopathological factors between two groups

	P-CRP	< 1.782	≥ 1.782	
		n = 49	*n* = 58	*P* value
Age (years)		72 ± 8.1	73.5 ± 8.6	0.53
Sex	Male	29	39	0.43
	Female	20	19	
BMI (kg/m^2)		21.4 ± 3	21.9 ± 3.18	0.26
PS	0	33	36	0.69
	1/2	16	22	
Tumor location	Head	28	39	0.32
	Body/Tail	21	19	
Preoperative Infection	Yes	3	10	0.14
	No	46	48	
NAC	Yes	6	7	1
	No	43	51	
AC	Yes	25	29	1
	No	24	29	
Operation time (h)		7.5 ± 2.5	8.3 ± 2.4	0.047*
Blood loss (g)		390 ± 569	578 ± 587	0.028*
PVR	Yes	12	11	0.64
	No	37	47	
R0	Yes	42	48	0.79
	No	7	10	
Stage	0/I/II	48	57	1
	III/IV	1	1	
Histology	PDAC	40	46	0.81
	Others (including IPMC)	9	12	
T stage	Tis/1/T	9	6	0.27
	3/4	40	52	
N stage	N0	27	22	0.084
	N1	22	36	
Vascular invasion	Yes	38	49	0.46
	No	11	9	
Perinural invasion	Yes	40	50	0.6
	No	9	8	
Lympho invasion	Yes	3	10	0.14
	No	46	48	
POPF ≥ grade B	Yes	8	18	0.11
	No	41	40	
Complication CD ≥ 2	Yes	13	23	0.22
	No	36	35	

*Statistically significant.
AC, adjuvant chemotherapy; BMI, body mass index; CD, Clavien-Dindo Classification; NAC, neoadjuvant chemotherapy; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula; PS, performance status; PVR, portal vein resection.

Table 3. Relationships between clinicopathological factors and OS in PC patients

		n	5Y survival (%)	MST (year)	*P* value
Age (years)	< 65	23	40	3.11	0.61
	≥ 65	84	28	2.38	
Sex	Female	39	38	3.11	0.1
	Male	68	26	2.37	
BMI	< 25	92	31	2.38	0.63
	≥ 25	15	27	3.11	
PS	0	69	36	3.11	0.0018*
	1/2	38	20	1.37	
Tumor location	Head	67	33	2.93	0.96
	Body/Tail	40	26	2.38	
Preoperative Infection	0	94	31	2.48	0.53
	1	13	<NA>	2.05	
NAC	Yes	13	34	3.30	0.64
	No	94	30	2.38	
AC	Yes	54	27	2.48	0.68
	No	53	34	2.48	
Operation time	≤ 8 h	58	35	1098	0.091
	> 8 h	49	25	798	
Blood loss	≤ 500 g	55	36	1190	0.05
	> 500 g	52	25	798	
PVR	Yes	23	37	2.37	0.96
	No	84	29	2.48	
R0	Yes	90	29	2.48	0.68
	No	17	<NA>	1.72	
UICC	0 /I/II	105	31	2.48	0.025*
	III/IV	2	<NA>	0.98	
Histology	PDAC	86	29	2.48	0.96
	Others (including IPMC)	21	46	2.38	
pT	Tis/1/2	15	75	<NA>	0.0045*
	3/4	92	25	2.33	
pN	0	49	52	10.07	< 0.001*
	1	58	12	1.52	
POPF ≥ grade B	Yes	26	47	3.62	0.19
	No	81	25	2.37	
complication CD ≥ 2	Yes	36	26	2.38	0.3
	No	71	39	3.30	
P-CRP	≤ 1.782	49	38	3.26	0.019*
	> 1.782	58	24	2.15	
CEA (ng/mL)	< 5	81	32	2.93	0.092
	≥ 5	26	26	1.27	
CA19-9 (U/mL)	< 35	50	36	3.11	0.021*
	≥ 35	57	26	1.83	

*Statistically significant.
5Y survival, 5 year survival; AC, adjuvant chemotherapy; BMI, body mass index; CD, Clavien-Dindo Classification; IPMC, intraductal papillary mucinous carcinoma; MST, median survival time; NA, not applicable; NAC, neoadjuvant chemotherapy; OS, overall survival; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula; PS, performance status; PVR, portal vein resection.

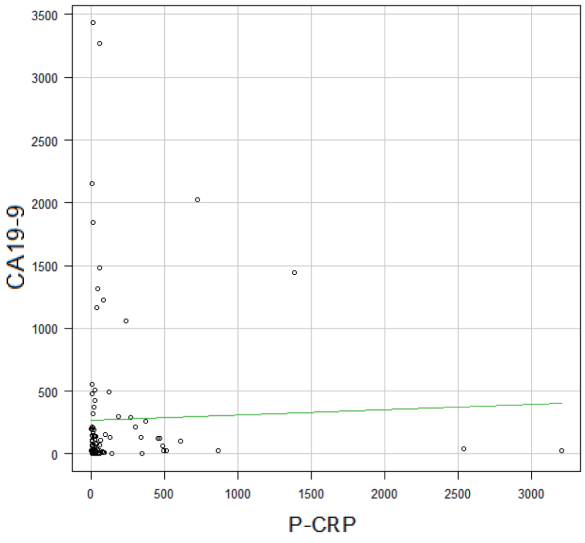

Fig. 2. No significant correlation between P-CRP and CA19-9 (Pearson's $R = 0.029$, $P = 0.77$).

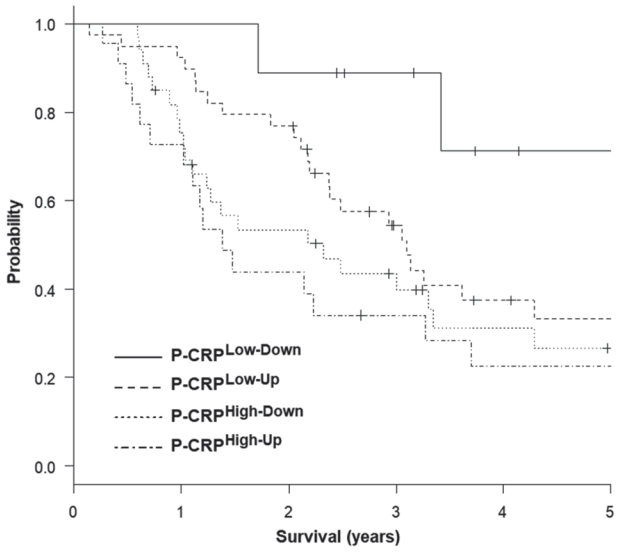

Fig. 3. Survival curves for OS in four groups; P-CRP$^{\text{Low-Down}}$, P-CRP$^{\text{Low-Up}}$, P-CRP$^{\text{High-Down}}$ and P-CRP$^{\text{High-Up}}$. The four groups had significant difference in prognosis ($P = 0.012$).

Table 4. Multivariate analysis for OS

	HR	95% CI	*P* value
T3/T4	2.503	0.58–10.71	0.22
pN	2.816	1.589–4.99	< 0.001*
PS	1.471	0.852–2.542	0.17
P-CRP	1.001	1–1.001	0.003*
CA19-9 (U/mL)	1.001	1–1.001	< 0.001*

*Statistically significant.
CI, confidence interval; HR, hazard ratio; OS, overall survival; PS, performance status.

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