

**ORIGINAL****Value of the fibrinogen–platelet ratio in patients with resectable pancreatic cancer**

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**Abstract : Background :** Several prognostic factors were reported in pancreatic cancer. The fibrinogen–platelet ratio (FPR) was reported as a prognostic factor of resectable gastric cancer. In this report, the FPR was evaluated in patients with resectable pancreatic cancer. **Methods :** Between 2004 and 2019, 163 patients with curative resection for pancreatic cancer were enrolled. Cases of non-curative resection were excluded. The FPR was calculated using the preoperative plasma fibrinogen and the platelet counts and the cut-off value was determined by receiver operating characteristic (ROC) curve analysis. The patients were divided into high and low FPR groups according to this cut-off value. **Results :** The cut-off value of FPR was 25.2. Among age, sex, body mass index (BMI), and surgical factors including surgery type, volume of blood loss and surgery time, there was no significant difference between the two groups. Patients in the low FPR group had significantly better overall survival (OS) and relapse-free survival (RFS) compared with the high FPR group ( $P < 0.05$ ). On multivariate analysis, a high FPR, CA19-9  $> 300$  U/ml, and receipt of adjuvant chemotherapy were independent risk factors for OS and DFS. **Conclusions :** The FPR might be a prognostic factor for patients with resectable pancreatic cancer. *J. Med. Invest.* 68:342-346, August, 2021

**Keywords :** fibrinogen, platelets, pancreatic cancer

**INTRODUCTION**

The prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) is extremely poor. In the United States, the 5-year overall survival rate is only 8% (1). Surgical resection is an effective treatment procedure for PDAC. Nowadays, adjuvant chemotherapy has been recommended for pathological stage more than II after surgical resection in Japan (2). However, the rate of recurrence after surgery is still high. Therefore, to administer adjuvant chemotherapy and understand the mechanism of cancer progression, novel predictive markers for postoperative survival and recurrence are required.

Various studies were performed to identify appropriate molecular biomarkers for prediction of postoperative prognosis. Several predictive markers based on immune-nutritional status were reported, including the neutrophil–lymphocyte ratio (NLR), the platelet–lymphocyte ratio (PLR), and the prognostic nutritional index (PNI) (3, 4).

Coagulation system disorders are frequently observed in patients with malignancies, and these disorders, including those that activate platelets, are associated with poor prognosis (5, 6). Recently, Wakatsuki *et al.* reported that the fibrinogen–platelet ratio (FPR) is a poor prognostic factor of overall survival (OS) and relapse-free survival (RFS) in stage II/III gastric cancer patients (7). Furthermore, Watanabe *et al.* reported the multiplication of d-dimer, which is a fibrin-cleaved product in platelets that can predict postoperative recurrence and prognosis for patients with cholangiocarcinoma (8).

The aim of this study was to clarify the impact of fibrinogen

and platelets as prognostic markers after curative resection for patients with pancreatic cancer using the FPR.

**PATIENTS AND METHODS**

One hundred sixty-three patients who underwent curative surgical resection for PDAC during 2004 to 2019 at the University of Tokushima Hospital were enrolled in this retrospective study. Fourteen patients were excluded because of non-curative (R2) resection which meant macroscopic residual tumor and distant metastasis. All patients had PDAC proven histologically. Finally, 149 patients were analyzed in this study. Laboratory data including serum fibrinogen, platelet, C-reactive protein (CRP), and albumin were collected within 1 month before surgery. Patients were followed up monthly for tumor markers including CEA and CA19-9 and underwent computed tomography every 4–6 months. When recurrence was suspected, precise diagnostic imaging studies including positron emission tomography were performed. After confirmation of recurrent pancreatic cancer, systemic chemotherapy, radiation therapy, or best supportive care were indicated. All patients signed informed consent for this study, which was approved by the clinical ethics committee at University of Tokushima Institution-Review Board (#3325). This study has been reported in line with the strengthening the reporting of cohort studies in surgery criteria (9).

The NLR, PNI, PLR, and modified Glasgow prognostic score (mGPS) were calculated and the cutoff values were 3, 45, 150, and 1, respectively. The fibrinogen–platelet ratio was calculated.

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**Abbreviations**

PDAC, pancreatic ductal adenocarcinoma ; NLR, neutrophil–lymphocyte ratio ; PLR, platelet–lymphocyte ratio ; PNI, prognostic nutritional index ; FPR, fibrinogen–platelet ratio ; OS, overall survival ; RFS, relapse-free survival ; ROC, receiver operation characteristic ; CRP, C-reactive protein ; mGPS, modified Glasgow prognostic score ; HR, hazard ratio ; CI, confidential interval

To determine the appropriate cutoff value of the FPR, receiver operating characteristic (ROC) curve analysis was performed. The cutoff value of the FPR was 25.2 and the AUC value was 0.54223. The clinicopathological characteristics of the patients are shown in Table 1.

*Statistical analysis*

Statistical comparisons for significance were made using chi-squared test or Fisher’s exact test with one degree of freedom, as appropriate. Cumulative OS and RFS were determined using the Kaplan–Meier method with a log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazard model. A *p*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with JMP 14 software (SAS Institute, Cary, NC, USA).

**RESULTS**

*Comparison of prognostic factors for OS in patients with surgical resection for PDAC*

The OS rate was significantly worse in patients with a high FPR compared with those with a low FPR (Figure 1A). The prognostic factors for OS in patients with surgical resection for PDAC are shown in Table 2. In the univariate analysis, seven factors were independent prognostic factors for OS including FPR (hazard ratio (HR) 2.256, 95% confidence interval (CI) 1.392–3.659, *P* < 0.001), PNI (HR 2.250, 95% CI 1.384–3.645, *P* = 0.007), PLR (HR 1.643, 95% CI 1.022–2.684, *P* = 0.0045), CA19-9 (HR 2.085, 95% CI 1.314–3.311, *P* = 0.0013), adjuvant chemotherapy (HR 2.208, 95% CI 1.396–3.491, *P* = 0.0022), T3+4 (HR 2.873, 95% CI 1.700–5.114, *P* < 0.001), lymph node metastasis (HR 1.846, 95% CI 1.143–2.945, *P* = 0.0095) and resection margin R0 (HR 1.700, 95% CI 1.018-2.751, *P* = 0.0331). In multivariate analysis of these eight factors, three were independent prognostic factors for OS including FPR (HR 2.013, 95% CI 1.202–3.370), CA19-9 (HR 1.687, 95% CI 1.033–2.753), and adjuvant chemotherapy (HR 2.329, CI 1.435–3.781).

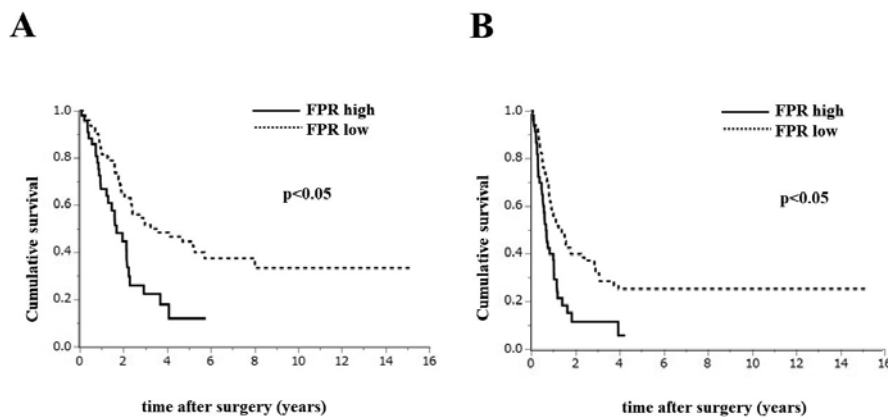
*Comparison of prognostic factors for RFS in patients with surgical resection for PDAC*

The RFS was significantly worse in patients with a high FPR compared with those with a low FPR (Figure 1B). The prognostic factors for RFS with surgical resection for PDAC are shown in Table 3. In the univariate analysis, five factors were independent prognostic factors for OS including FPR (HR 1.958, 95% CI 1.282–2.990, *P* = 0.0015), PNI (HR 1.542,

**Table 1.** Clinicopathological characteristics of patients with surgical resection for PDAC

Parameters	
Age, years	70 (63-76)
female / male	77 (51.3) / 72 (48.7)
Body mass index kg/m <sup>2</sup>	22.1 (19.7-24.2)
Fibrinogen, g/ml	439 (367-510)
C reactive protein, mg/L	0.09 (0.05-0.27)
Serum albumin, g/dl	3.9 (3.7-4.2)
WBC, 10 <sup>9</sup> /L	5450 (4400-6600)
Neutrophils, 10 <sup>9</sup> /L	3650 (2600-4495)
Lymphocytes, 10 <sup>9</sup> /L	1290 (1040-1715)
CEA ng/ml	2.3 (1.4-3.9)
CA19-9 U/ml	126 (27.5-670)
Type of resection (DP/PD/TP)	46/98/5
PV resection (n, %)	22 (14.7)
Neoadjuvant chemotherapy (n, %)	16 (10.7)
Postoperative chemotherapy (n, %)	89 (59.3)
UICC stage (n, %)	
I A	20 (15.4)
I B	16 (16)
II A	47 (31.5)
II B	43 (28.9)
III	23 (15.4)
Resection margin R0	115 (76.7)
Tumor size ≥ 2 cm	113 (75.6)
Lymph node metastasis (n)	52 (35.1)
Lymphatic invasion (ly)	100 (68.0)
Vascular invasion (v)	114 (77.6)
Perineural invasion (ne)	119 (81.5)
Anterior serosal invasion (s)	34 (29.6)
Retroperitoneal invasion (rp)	45 (38.1)
Microscopic portal vein invasion (pv)	23 (22.3)
Microscopic arterial invasion (a)	6 (5.7)
Plexus invasion (pl)	11 (12.5)

Data are expressed as median (IQR) or n(%)  
 DP : distal pancreatectomy, PD : pancreaticoduodenectomy, TP : total pancreatectomy, PV : portal vein resection



**Figure 1.** Kaplan–Meier curves of overall survival and disease-free survival according to the FPR. (A) Overall survival. (B) Relapse-free survival.

**Table 2.** Comparison of prognostic factors for overall survival (OS) in patients with surgical resection for pancreatic ductal adenocarcinoma

Factor		Univariate		Multivariate	
		p-value	HR (95% CI)	p-value	HR (95% CI)
Age	< 70/ ≥ 70	0.1558	1.391 (0.874-2.201)		
Gender	female/male	0.7023	1.315 (0.829-2.087)		
BMI kg/m <sup>2</sup>	< 25/ ≥ 25	0.5203	1.216 (0.639-2.143)		
T(3+4)	No / yes	< 0.001	2.873 (1.700-5.114)	0.0919	1.713 (0.916-3.203)
N(+)	No / yes	0.0095	1.846 (1.143-2.945)	0.1459	1.459 (0.882-2.415)
Resection type	PD/DP/TP	0.4474	1.190 (0.726-1.951)		
Resection margin	R0 / R1	0.0331	1.700 (1.018-2.751)	0.1878	1.428 (0.840-2.428)
PV resection	No / yes	0.4731	1.310 (0.575-2.600)		
NAC(-)	No / yes	0.9223	1.039 (0.433-2.116)		
AC(-)	No / yes	0.0022	2.208 (1.396-3.491)	0.0006	2.329 (1.435-3.781)
CEA ng/ml	< 5/ ≥ 5	0.5878	1.203 (0.578-2.248)		
CA19-9 U/ml	< 300/ ≥ 300	0.0013	2.085 (1.314-3.311)	0.0364	1.687 (1.033-2.753)
NLR	< 3/ ≥ 3	0.941	1.021 (0.603-1.672)		
PNI	< 45/ ≥ 45	0.0007	2.250 (1.384-3.645)	0.1867	1.397 (0.815-2.415)
PLR	< 150/ ≥ 150	0.0045	1.643 (1.022-2.684)	0.4714	1.219 (0.711-2.089)
mGPS	0 / 1,2	0.6799	2.270 (0.806-5.190)		
FPR	< 25.2/ ≥ 25.2	< 0.001	2.256 (1.392-3.659)	0.0078	2.013 (1.202-3.370)

DP : distal pancreatectomy, PD : pancreaticoduodenectomy, TP : total pancreatectomy, PV : portal vein resection, NAC : neoadjuvant chemotherapy, AC : adjuvant chemotherapy

**Table 3.** Comparison of prognostic factors for relapse-free survival (RFS) in patients with surgical resection for pancreatic ductal adenocarcinoma

Factor		Univariate		Multivariate	
		p-value	HR (95% CI)	p-value	HR (95% CI)
Age > 70	< 70/ ≥ 70	0.4904	1.176 (0.780-1.759)		
Gender (F/M)	Female/male	0.9196	1.040 (0.698-1.553)		
BMI > 25 kg/m <sup>2</sup>	< 25/ ≥ 25	0.3700	1.295 (0.729-2.158)		
T(3+4)	No/yes	0.0032	1.890 (1.232-2.966)	0.0536	1.596 (0.993-2.574)
N(+)	No/yes	0.0561	1.494 (0.979-2.252)		
Resection type	PD/DP/TP	0.4415	1.322 (0.850-2.058)		
Resection margin	R0 / R1	0.1576	1.382 (0.865-2.141)		
PV resection	No/yes	0.1937	1.466 (0.809-2.478)		
NAC(-)	No/yes	0.4135	1.306 (0.709-2.405)		
AC(-)	No/yes	0.0020	1.884 (1.257-2.824)	0.0020	1.923 (1.269-2.916)
CEA > 5 ng/ml	< 5/ ≥ 5	0.1032	1.604 (0.886-2.713)		
CA19-9 > 300 U/ml	< 300/ ≥ 300	0.0031	1.864 (1.239-2.797)	0.0150	1.686 (1.107-2.569)
NLR	< 3/ ≥ 3	0.3812	1.176 (0.759-1.792)		
PNI	< 45/ ≥ 45	0.0308	1.542 (1.008-2.340)	0.5538	1.146 (0.730-1.797)
PLR	< 150/ ≥ 150	0.2235	1.270 (0.840-1.928)		
mGPS (0/1+2)	0 / 1,2	0.0529	1.956 (0.662-4.642)		
FPR	< 25.2/ ≥ 25.2	0.0015	1.958 (1.282-2.990)	0.0029	1.967 (1.259-3.072)

DP : distal pancreatectomy, PD : pancreaticoduodenectomy, TP : total pancreatectomy, PV : portal vein resection, NAC : neoadjuvant chemotherapy, AC : adjuvant chemotherapy

95% CI 1.008–2.340,  $P = 0.0308$ ), CA19-9 (HR 1.864, 95% CI 1.239–2.797,  $P = 0.0031$ ), adjuvant chemotherapy (HR 1.884, 95% CI 1.257–2.824,  $P = 0.0020$ ), and T(3+4) (HR 1.890, 95% CI 1.232–2.966,  $P = 0.0032$ ). In the multivariate analysis of these five factors, three were independent prognostic factors for RFS including FPR (HR 1.967, 95% CI 1.259–3.072,  $P = 0.0029$ ), CA19-9 (HR 1.686, 95% CI 1.107–2.569,  $P = 0.0150$ ), and adjuvant chemotherapy (HR 1.923, 95% CI 1.269–2.916,  $P = 0.0020$ ).

#### Clinicopathological features according to the FPR

Clinicopathological factors are compared between the high and low FPR groups in Table 4. Among the tumor-related factors, the high FPR group was significantly correlated with neo-adjuvant chemotherapy and T(3+4). Also, the high FPR group showed an association with portal vein resection but was not statistically significant. The other factors showed no significant differences between these two groups.

**Table 4.** Clinicopathological features according to fibrinogen and platelet ratio

Factor	FPR High (n=47)	FPR Low (n=102)	p-value
Age $\geq 70$ / <70	21 / 26	50 / 52	0.6219
Male / Female	24 / 23	48 / 54	0.6494
BMI $\text{kg}/\text{m}^2 \geq 25$ / <25	5 / 42	17 / 85	0.3230
T 3+4 / 1+2	37 / 10	38 / 64	0.0474
N -/+	16 / 31	36 / 66	0.2373
DP / PD / TP	18 / 27 / 2	28 / 71 / 3	0.3532
PV resection -/+	36 / 11	90 / 12	0.0753
NAC -/+	38 / 9	95 / 7	0.0317
AC -/+	25 / 22	38 / 64	0.2709
CEA $\text{ng}/\text{ml}$ , $\geq 5$ / <5	8 / 39	14 / 88	0.6183
CA19-9 $\text{U}/\text{ml}$ , $\geq 300$ / <300	14 / 33	43 / 59	0.1448
Alb $\geq \text{g}/\text{dl}$ , 3.5 / <3.5	41 / 6	80 / 22	0.2012

BMI : body mass index, DP : distal pancreatectomy, PD : pancreaticoduodenectomy, TP : total pancreatectomy, PV : portal vein, NAC : neoadjuvant chemotherapy, AC : adjuvant chemotherapy, Alb : albumin

## DISCUSSION

In this study, a FPR value of more than 25.2 was a post-operative poor prognostic factor for patients with PDAC. The high FPR group showed a higher T stage and frequency of portal vein resection and was associated with local aggressiveness of PDAC. Serum fibrinogen and platelet number were measured in most of the patients, and thus FPR was calculated easily.

In several reports, hemostatic status was associated with poor prognosis in PDAC. Zhang *et al.* reported that prolonged prothrombin time, high fibrinogen, and mean platelet volume were independent prognostic factors for poor OS in patients with advanced metastatic pancreatic cancer (10). The occurrence of venous thromboembolic disease is associated with reduced response rate of chemotherapy and a shorter OS and DFS among the patients with advanced pancreatic cancer in various stage (11, 12). Hyperfibrinogen is associated with the systemic inflammatory response and predict poor prognosis for advanced pancreatic cancer (13). Preoperative fibrinogen and high NLR are also associated with poor prognosis in resectable breast cancer (14).

In the current study, patients with distant metastasis such as

liver, lung, and peritoneal dissemination were excluded. Tumor diameter, lymph node metastasis, histological differentiation, and adjuvant chemotherapy were reported as poor prognostic factors following curative resection for PDAC (15). The migration, invasion, and metastasis of cancer cells can contribute to inflammation through the activation of several chemokines such as CXCR4 and its ligand CXCL12 (16). We speculated that the local inflammation caused by local cancer invasion was correlated with the coagulation status of patients with PDAC ; therefore, the FPR could reflect this local inflammation.

Platelets contribute to cancer progression and metastasis through six hallmarks : sustaining proliferative signals, resisting cell death, inducing angiogenesis, evading immune detection, and supporting cancer stem cells. Antiplatelet therapies might be a new candidate for anticancer therapy (17). Thrombocytosis was observed and reported as a poor prognostic factor for various types of cancer including PDAC (18).

Fibrinogen synthesized from hepatocytes is converted to fibrin through thrombin and factor VIII. Fibrin forms platelet plugs in the wound site. The relationship between platelets and fibrinogen in cancer was associated with stromal formation, angiogenesis, and hematogenous metastasis (19, 20). In basic research using a fibrinogen knock-out and platelet-inactivated animal model, metastasis of embryonic tumor cells was significantly decreased. Moreover, platelet and fibrinogen deposition was found to be crucial for vascular endothelial adhesion and evasion from NK cell-mediated elimination of cancer cells (21). The FPR may be associated with these roles of platelets and fibrinogen in cancer progression.

There were several limitations in this study. It was retrospective study and the sample size was relatively small. Further prospective studies using more samples or propensity score matching are required.

In conclusion, the preoperative FPR is a poor prognostic factor in patients with resectable PDAC. FPR can be calculated easily using preoperative serum fibrinogen and platelet values and might reflect local inflammation caused by invasion of PDAC.

## AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## CONTRIBUTIONS

YA, KM, MY, SY, YS, TI, SI, YM and MS : substantial contributions to the conception, or design of the work ; or the acquisition, analysis or interpretation of data ; or have drafted the work or substantively revised it. YA, KM, MY, SY, YS, TI, SI, YM and MS : have approved the submitted version.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of University of Tokushima, Tokushima, Japan (#3325). It followed the ethical principles (as revised in 2013) of the Helsinki Declaration.

## CONSENT FOR PUBLICATION

Not applicable.

## CONSENT FOR PUBLICATION

The authors declare that they have no competing interests.

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