**ORIGINAL**

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

Yusuke Arakawa, M.D, Katsuki Miyazaki, M.D, Masato Yoshikawa, M.D, Shinichirou Yamada, M.D, Yu Saito, M.D, Tetsuya Ikemoto, M.D, Satoru Imura, M.D, Yuji Morine, M.D and Mitsuo Shimada, M.D, PhD

*Department of Digestive Surgery and Transplantation, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan*

**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.

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

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Address correspondence and reprint requests to Yusuke Arakawa, Department of Surgery, Tokushima University Graduate School of Biomedical Sciences, 3-18-15 Kuramoto-cho, Tokushima, 770-8503, Japan and Fax : +81-88-631-9698.

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$^2$ | 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$^9$/L | 5450 (4400-6600) |
| Neutrophils, 10$^9$/L | 3650 (2600-4495) |
| Lymphocytes, 10$^9$/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, %) | |
| ⅠA | 20 (15.4) |
| ⅠB | 16 (16) |
| ⅡA | 47 (31.5) |
| ⅡB | 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 : pancreaticoduodenctomy, TP : total pancreatectomy, PV : portal vein resection

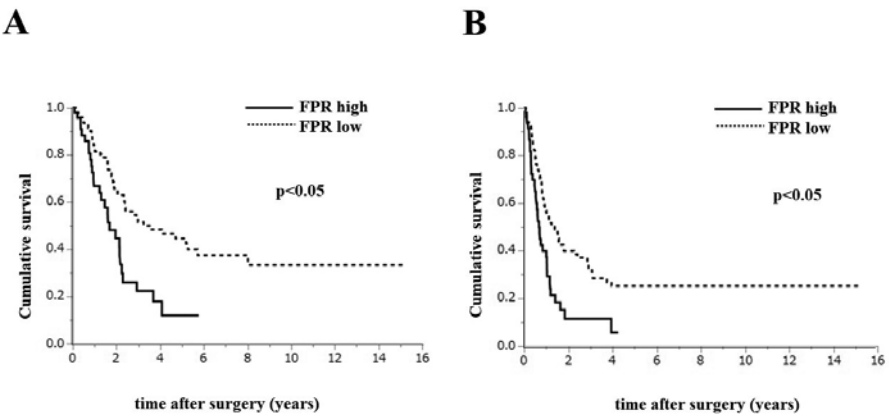


Figure 1. Kaplan–Meier curves of overall survival and disease-free survival according to the FPR. (A) Overall survival. (B) Relapse-free survival.

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

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| Factor | | 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$^2$ | <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 : pancreaticoduodenctomy, 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

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| Factor | | 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$^2$ | <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 : pancreaticoduodenctomy, 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 neoadjuvant 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 ≥70 / <70 | 21 / 26 | 50 / 52 | 0.6219 |
| Male / Female | 24 / 23 | 48 / 54 | 0.6494 |
| BMI kg/m$^2$ ≥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 ng/ml, ≥5 / <5 | 8 / 39 | 14 / 88 | 0.6183 |
| CA19-9 U/ml, ≥300 / <300 | 14 / 33 | 43 / 59 | 0.1448 |
| Alb ≥ g/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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## AUTHOR INFORMATION

Affiliation : Department of Digestive Surgery and Transplantation, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

## 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.

## REFERENCES

1. Siegel RL, Miller KD, Jemal A : Cancer statistics, 2018. CA Cancer J Clin 68(1) : 7-30, 2018
2. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, Kaneoka Y, Shimizu Y, Nakamori S, Sakamoto H, Morinaga S, Kainuma O, Imai K, Sata N, Hishinuma S, Ojima H, Yamaguchi R, Hirano S, Sudo T, Ohashi Y, JASPAC 01 Study Group : Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer : a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet 388(10041) : 248-257, 2016
3. Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A : Nutritional predictors of postoperative outcome in pancreatic cancer. The British journal of surgery 98(2) : 268-274, 2011
4. Sierzega M, Lenart M, Rutkowska M, Surman M, Mytar B, Matyja A, Siedlar M, Kulig J : Preoperative Neutrophil-Lymphocyte and Lymphocyte-Monocyte Ratios Reflect Immune Cell Population Rearrangement in Resectable Pancreatic Cancer. Annals of surgical oncology 24(3) : 808-815, 2017
5. Goldenberg N, Kahn SR, Solymoss S : Markers of coagulation and angiogenesis in cancer-associated venous thromboembolism. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 21(22) : 4194-4199, 2003
6. Gay LJ, Felding-Habermann B : Contribution of platelets to tumour metastasis. Nature reviews Cancer 11(2) : 123-134, 2011
7. Wakatsuki K, Matsumoto S, Migita K, Kunishige T, Nakade H, Miyao S, Sho M : Prognostic value of the fibrinogen-to-platelet ratio as an inflammatory and coagulative index in patients with gastric cancer. Surgery today 49(4) : 334-342, 2019
8. Watanabe A, Araki K, Hirai K, Kubo N, Igarashi T, Tsukagoshi M, Ishii N, Hoshino K, Kuwano H, Shirabe K : A Novel Clinical Factor, D-Dimer Platelet Multiplication, May Predict Postoperative Recurrence and Prognosis for Patients with Cholangiocarcinoma. Annals of surgical oncology 23(Suppl 5) : 886-891, 2016
9. Agha R, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C, Mathew G, Group S : STROCSS 2019 Guideline : Strengthening the reporting of cohort studies in surgery. Int J Surg 72 : 156-165, 2019
10. Zhang K, Gao HF, Mo M, Wu CJ, Hua YQ, Chen Z, Meng ZQ, Liu LM, Chen H : A novel scoring system based on hemostatic parameters predicts the prognosis of patients with advanced pancreatic cancer. Pancreatology 19(2) : 346-351, 2019
11. Frere C, Bournet B, Gourgou S, Fraisse J, Canivet C, Connors JM, Buscail L, Farge D, Consortium B : Incidence of Venous Thromboembolism in Patients With Newly Diagnosed Pancreatic Cancer and Factors Associated With Outcomes. Gastroenterology 158(5) : 1346-1358 e1344, 2020
12. Mandala M, Reni M, Cascinu S, Barni S, Floriani I, Cereda S, Berardi R, Mosconi S, Torri V, Labianca R : Venous thromboembolism predicts poor prognosis in irresectable pancreatic cancer patients. Annals of oncology : official journal of the European Society for Medical Oncology/ESMO 18(10) : 1660-1665, 2007
13. Qi Q, Geng Y, Sun M, Chen H, Wang P, Chen Z : Hyperfibrinogen Is Associated With the Systemic Inflammatory Response and Predicts Poor Prognosis in Advanced Pancreatic Cancer. Pancreas 44(6) : 977-982, 2015
14. Cao X, Zhou Y, Mao F, Lin Y, Sun Q : Combination of preoperative fibrinogen concentration and neutrophil-to-lymphocyte ratio for prediction of the prognosis of patients with resectable breast cancer. Oncol Lett 20(5) : 200, 2020
15. Lim JE, Chien MW, Earle CC : Prognostic factors following curative resection for pancreatic adenocarcinoma : a population-based, linked database analysis of 396 patients. Annals of surgery 237(1) : 74-85, 2003
16. Mantovani A, Allavena P, Sica A, Balkwill F : Cancer-related inflammation. Nature 454(7203) : 436-444, 2008
17. Franco AT, Corken A, Ware J : Platelets at the interface of thrombosis, inflammation, and cancer. Blood 126(5) : 582-588, 2015
18. Ikeda M, Furukawa H, Imamura H, Shimizu J, Ishida H, Masutani S, Tatsuta M, Satomi T : Poor prognosis associated with thrombocytosis in patients with gastric cancer. Annals of surgical oncology 9(3) : 287-291, 2002
19. Palumbo JS, Kombrinck KW, Drew AF, Grimes TS, Kiser JH, Degen JL, Bugge TH : Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. Blood 96(10) : 3302-3309, 2000
20. Zhao LY, Zhao YL, Wang JJ, Zhao QD, Yi WQ, Yuan Q, Chen XZ, Li Y, Yang K, Chen XL, Zhang WH, Liu K, Pang HY, Galiullin D, Wang H, Sun LF, Song XH, Zheng JB, Yao XQ, Zhou ZG, Yu PW, Hu JK : Is Preoperative Fibrinogen Associated with the Survival Prognosis of Gastric Cancer Patients? A Multi-centered, Propensity Score-Matched Retrospective Study. World journal of surgery 44(1) : 213-222, 2020
21. Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW, Jirouskova M, Degen JL : Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood 105(1) : 178-185, 2005