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ORIGINAL ARTICLE

Retrospective Study

Combination of preoperative fibrinogen and D-dimer as a prognostic indicator in pancreatic ductal adenocarcinoma patients undergoing R0 resection

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Author contributions: Zhang LP was involved in study conception, data analysis, and production of tables, wrote the first draft, and revised it critically in light of comments from other authors; Ren H, Du YX and Zheng XH helped to collect the clinical data and followed up with the patients; Wang CF and Zhang ZM were involved in study conception and design, data interpretation, manuscript revision, and discussion; all authors approved the final version submitted.

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Abstract

BACKGROUND

Patients with malignant tumors frequently exhibit hyperactivation of the coagulation system and secondary increased fibrinolytic activity. Fibrinogen and D-dimer are common indicators that are crucial in the coagulation/fibrinolysis system. Both indicators have been verified to have predictive value in the overall survival (OS) of many patients with solid malignancies.

AIM

To explore the prognostic significance of fibrinogen combined with D-dimer in pancreatic ductal adenocarcinoma (PDAC) patients undergoing radical R0 resection.

METHODS

We retrospectively analyzed the clinical data of 282 patients with PDAC undergoing radical R0 resection in the Cancer Hospital, Chinese Academy of Medical Sciences, between January 2010 and December 2019. The surv_cutpoint function of R language was used to determine the optimal cutoff values of the

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preoperative fibrinogen concentration and preoperative D-dimer concentration. Enrolled patients were further divided into the any-high group (high preoperative fibrinogen concentration and/or high preoperative D-dimer concentration) and the low-low group (low preoperative fibrinogen and D-dimer concentrations) according to the optimal cutoff values.

RESULTS

The optimal cutoff values of the preoperative fibrinogen concentration and preoperative D-dimer concentration were 3.31 g/L and 0.53 mg/L, respectively. Furthermore, multivariate Cox regression analysis showed that the preoperative fibrinogen concentration (HR: 1.603, 95%CI: 1.201-2.140, P = 0.001) and preoperative D-dimer concentration (HR: 1.355, 95%CI: 1.019-1.801, P = 0.036) exhibited obvious correlations with the OS of PDAC patients undergoing radical R0 resection. A prognostic analysis was further performed based on the subgroup results by using fibrinogen combined with D-dimer. The median OS duration of the low-low group (31.17 mo) was significantly longer than that of the any-high group (15.43 mo). Additionally, multivariate Cox regression analysis revealed that the degree of differentiation (P < 0.001), lymph node metastasis (HR: 0.663, 95%CI: 0.497-0.883, P = 0.005), preoperative CA19-9 level (HR: 1.699, 95%CI: 1.258-2.293, P = 0.001), adjuvant therapy (HR: 1.582, 95%CI: 1.202-2.081, P = 0.001) and preoperative combined grouping (HR: 2.397, 95%CI: 1.723-3.335, P < 0.001) were independent predictors of OS in PDAC patients undergoing radical R0 resection.

CONCLUSION

Preoperative fibrinogen combined with D-dimer plays a predictive role in OS, and low preoperative fibrinogen and D-dimer concentrations can indicate prolonged OS in PDAC patients undergoing radical R0 resection.

Key Words: Pancreatic ductal adenocarcinoma; R0 resection; Fibrinogen; D-dimer; Prognosis; Survival

Core Tip: Both fibrinogen and D-dimer have been demonstrated to be independent predictors of overall survival (OS) in many patients with solid malignancies. We retrospectively analyzed the medical records of 282 patients with pancreatic ductal adenocarcinoma (PDAC) undergoing radical R0 resection. Our study confirms the synergistic value of fibrinogen and D-dimer in predicting OS, and low preoperative fibrinogen and D-dimer concentrations can indicate prolonged OS in PDAC patients undergoing radical R0 resection.

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INTRODUCTION

Pancreatic cancer (PC) is a digestive system tumor with a poor prognosis and almost equal morbidity and mortality rates[1]. It is the fourth leading cause of cancer-related death worldwide[2]. The 5-year survival rate of PC patients in the United States is only 10%[3]. In addition, it is estimated that PC will be the second leading cause of cancer-related death in the United States after lung cancer by 2030[4]. Radical resection has been accepted as an effective therapeutic choice that can significantly prolong the survival of patients with PC[5]; it helps to reduce the perioperative mortality and complications of patients who undergo pancreatic surgery[6]. However, there is no

significant improvement in the overall survival (OS) of patients with PC[7,8]. The poor prognosis of PC patients is reported to be associated with asymptomatic onset[9,10], and a high risk of distant metastasis in the early stage[11]. Consequently, nearly 80% of patients with PC have been in the middle-advanced stage when they are diagnosed and have lost the opportunity for radical surgery[12].

Patients with malignant tumors are generally in a hypercoagulable state, which leads to obvious thrombosis in the clinic[13,14]. Cancer-associated venous thromboembolism (VTE) has become the second leading cause of death after the tumor itself[15,16], and the incidence of VTE is as high as 36% in PC patients[17]. The occurrence and development of tumors can be promoted *via* the function of the coagulation/fibrinolysis system in a variety of ways[13].

In the final stage of normal coagulation, soluble fibrinogen can be hydrolyzed to form insoluble fibrin and constitutes the major part of the clot. Simultaneously, the fibrinolysis mechanism can be initiated *in vivo*, and fibrinolytic enzymes can decompose blood clots and produce fibrin degradation products, including D-dimer. Furthermore, fibrinogen is involved not only in the coagulation process but also in the systemic inflammatory response as an acute phase protein[18]. Inflammation has been documented as one of the most important characteristics of cancer[19]. In addition, as a common indicator with important value in the coagulation/fibrinolysis system, D-dimer can reflect the hyperactivity of the coagulation system and secondary increased fibrinolytic activity[20].

The significance of tumor-related degradation products of the coagulation/fibrinolysis system has always been a hot research topic when evaluating patient prognosis[21]. Elevated fibrinogen[22] or D-dimer[23] concentrations are associated with a poor prognosis in many solid malignancies. It has been proven that co-elevated fibrinogen and D-dimer concentrations are independent prognostic factors for short OS in patients with advanced liver cancer[24]. To date, there have been no reports on the correlation of the synergistic value of fibrinogen and D-dimer with the prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) undergoing radical R0 resection. In this regard, a retrospective study was carried out to investigate the prognostic value of preoperative fibrinogen combined with D-dimer in these patients.

MATERIALS AND METHODS

Patients and data collection

The study subjects were 282 PDAC patients undergoing radical R0 resection in the Cancer Hospital, Chinese Academy of Medical Sciences, between January 2010 and December 2019. The inclusion criteria were as follows: (1) Patients over 18 years old; (2) Patients with no distant metastasis confirmed by imaging examinations, including enhanced computed tomography (CT), enhanced magnetic resonance imaging, and positron emission tomography/CT; (3) Patients undergoing radical pancreaticoduodenectomy or distal pancreatectomy with splenectomy; (4) Patients with a postoperative pathological diagnosis of PDAC and confirmed with R0 resection (no tumor cells within 1 mm from the resection margins[25]); and (5) Patients with complete follow-up data. The exclusion criteria were as follows: (1) Patients who died in the perioperative period (within 1 mo after surgery); (2) Patients with a medical history of a malignant tumor or other malignancies at the same time; (3) Patients who received neoadjuvant therapy; (4) Patients who received anticoagulant treatment before surgery; (5) Patients who had a recent history of blood transfusion or complications of anemia and other blood system diseases; and (6) Patients with complications of liver disease or other inflammatory diseases (Figure 1).

The clinicopathological features of the enrolled patients consisted of age at primary diagnosis, sex, blood type, diabetes, smoking status, alcohol consumption, family history of cancer, clinical symptoms (jaundice, pain, digestive symptoms, weight loss, fatigue, *etc.*), open surgery approach, tumor information (tumor location, degree of differentiation, lymphovascular invasion, perineural invasion, capsular invasion, maximal tumor diameter, and lymph node metastasis), T stage, N stage, tumor, node and metastasis (TNM) stage, preoperative CA19-9 level, preoperative fibrinogen concentration, preoperative D-dimer concentration, and adjuvant therapy. The pathological staging of PDAC was defined according to the TNM staging system updated and published by the American Joint Commission on Cancer and Union International Center of Cancer (8th version).

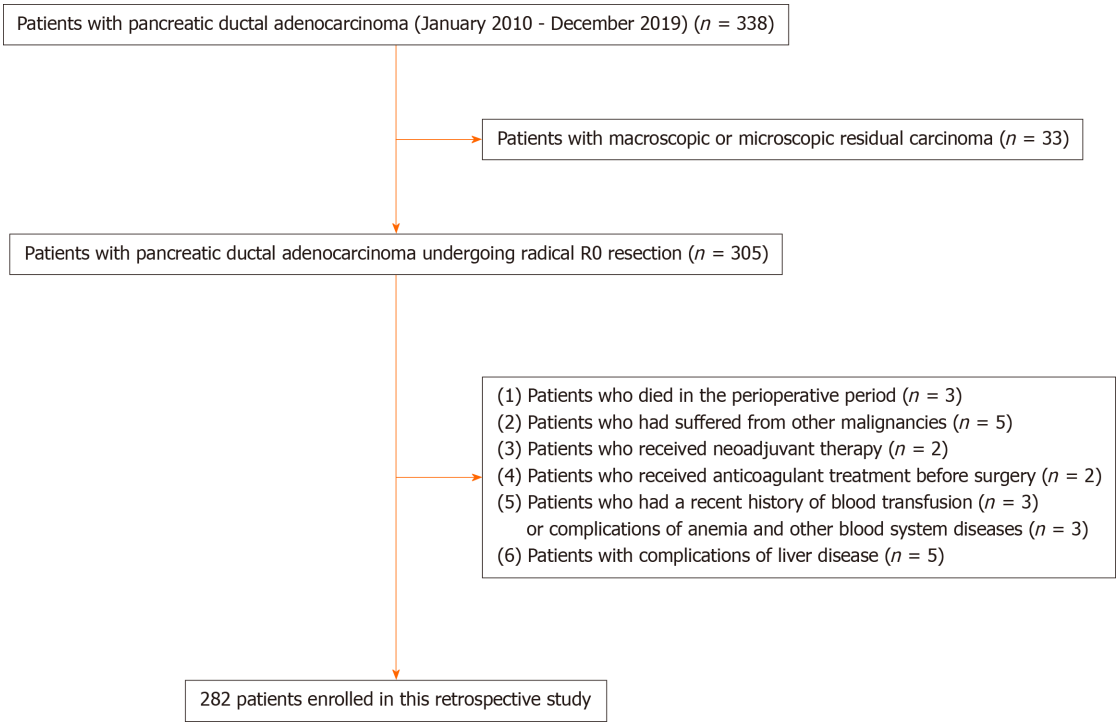

Figure 1 Flowchart of patient selection.

Ethical statement

The present study was conducted in strict accordance with the ethical standards of the Declaration of Helsinki of the World Medical Association. The study protocol was approved by the Medical Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences (approval No. 17-168/1424), and written informed consent was provided by all the enrolled patients.

Types of surgery

All the enrolled patients received radical surgery in our hospital. Patients with tumors in the head and neck of the pancreas underwent a pancreatoduodenectomy, also known as the Whipple procedure, the scope of surgical resection included pancreatic head and neck lesions, partial stomach, duodenum, partial jejunum, common bile duct and gallbladder. Patients with tumors located in the body and tail of the pancreas underwent distal pancreatectomy with splenectomy.

Laboratory measurements

Blood samples from all included patients were collected before breakfast within 7 d of surgery and detected rapidly on a CA7000 Analyzer (Sysmex Corporation, Kobe, Japan) in the laboratory to measure the concentrations of fibrinogen and D-dimer. The normal reference ranges of fibrinogen and D-dimer were 2.0-4.0 g/L and 0-0.50 mg/L, respectively.

Follow-up assessments

All patients were followed up effectively *via* approaches such as telephone calls every 3 mo within two years postoperatively and then every 6 mo. The date of surgery was defined as the beginning of the follow-up, and the last follow-up date was August 16, 2020. OS was defined as the period from the date of surgery to the date of death or the last follow-up.

Statistical analysis

Continuous data with normal distribution are expressed as the mean ± SD (Kolmogorov-Smirnov test, $P > 0.05$), while those with nonnormal distribution are expressed as the median (range: minimum-maximum). RStudio (version 1.3.1073, http://www.rstudio.org), SPSS (version 25.0; IBM Corp.), and Prism (version 8.02; GraphPad Software Inc.) were used for statistical analysis. The optimal cutoff values of the preoperative fibrinogen concentration and preoperative D-dimer concentration

were identified by the surv_cutpoint function of R language and verified by receiver operating characteristic (ROC) curve analysis. Categorical variables are presented as frequencies and percentages, and the χ^2 test and an independent samples *t*-test were used to compare variables. In addition, the cumulative survival rate was calculated with the Kaplan-Meier method, and the log-rank test was adopted to compare the difference in survival. A Cox proportional hazards model was used to evaluate prognostic variables for the multivariate analysis. The statistical results are expressed as the HRs and 95%CIs. A two-tailed $P < 0.05$ indicated the existence of a significant difference.

RESULTS

Patient characteristics

All 282 PDAC patients enrolled in this study underwent surgery in the Cancer Hospital, Chinese Academy of Medical Sciences. The median follow-up time of the included patients was 14.98 mo. Of the 282 patients, 217 died during the follow-up period, with a median OS duration of 17.43 mo (range: 1.30-100.07 mo). In addition, the 1-, 2-, 3-, and 5-year survival rates were 67.5%, 35.9%, 20.4% and 10.2%, respectively. Analysis of the clinical data of these patients showed that the median age at diagnosis was 61 years (age range: 31-81 years), and 136 (48.2%) patients were over 60 years old. Furthermore, of these patients, 131 (46.5%) were female; 225 (79.8%) had clinical symptoms, including jaundice, pain, digestive symptoms, weight loss, and fatigue; 130 (46.1%) underwent pancreatoduodenectomy, and the remaining 152 (53.9%) had tumors located in the body or tail of the pancreas; 121 (42.9%) had lymph node metastasis; and 158 (56.0%) received adjuvant therapy. Moreover, 217 (77.0%) patients were diagnosed with moderately differentiated adenocarcinoma by histopathology, and 29 (10.3%) patients were in stage III according to the 8th edition of the TNM staging standards. Table 1 lists the details of the baseline data of the included patients.

Determination of the optimal cutoff values for survival analysis

The surv_cutpoint function of R language was used to determine the optimal cutoff values of the preoperative fibrinogen concentration and preoperative D-dimer concentration, which were 3.31 g/L and 0.53 mg/L, respectively. The optimal cutoff values of the above indicators were also verified by their respective ROC curves (Figure 2).

The median preoperative fibrinogen concentration of all patients included in this study was 3.02 g/L (range: 1.20-6.70 g/L) (Table 1), and the optimal cutoff value was 3.31 g/L. As shown in Figure 2A, the area under the ROC curve (AUC) of preoperative fibrinogen was 0.714 (95%CI: 0.649-0.779), while the sensitivity and specificity at the maximal Youden's index were 61.14% and 79.37%, respectively. Based on this cutoff value, 141 (50.0%) patients had a preoperative fibrinogen concentration > 3.31/L, as described in Table 2.

Furthermore, the median preoperative D-dimer concentration of all enrolled patients was 0.52 mg/L (range: 0.12-582.00 mg/L) (Table 1), and the optimal cutoff value was 0.53 mg/L. The AUC of preoperative D-dimer was 0.753 (95%CI: 0.687-0.819) (Figure 2B), and the sensitivity and specificity at the maximal Youden's index were 58.78% and 78.82%, respectively. In addition, there were 165 (58.5%) patients with a preoperative D-dimer concentration ≤ 0.53 mg/L and 117 (41.5%) patients with a concentration > 0.53 mg/L, as indicated by the optimal cutoff value (Table 3).

Correlations of indicators with clinicopathological features

As presented in Table 2, patients enrolled in this study were divided into a low-concentration group (≤ 3.31 g/L) or a high-concentration group (> 3.31 g/L) according to the optimal cutoff value of the preoperative fibrinogen concentration. An increase in the preoperative fibrinogen concentration was obviously correlated with clinical symptoms ($P < 0.001$), open surgery approach ($P < 0.001$), tumor location ($P < 0.001$), preoperative CA19-9 level ($P = 0.023$) and preoperative D-dimer concentration ($P = 0.040$). However, no significant correlations were found between the preoperative fibrinogen concentration and age, sex, blood type, diabetes, smoking status, alcohol consumption, family history of cancer, degree of differentiation, lymphovascular invasion, perineural invasion, capsular invasion, maximal tumor diameter, T stage, lymph node metastasis, N stage, TNM stage, or adjuvant therapy. The Kaplan-Meier curve of preoperative fibrinogen revealed that the OS of patients with a preoperative

Table 1 Baseline characteristics of 282 pancreatic ductal adenocarcinoma patients undergoing radical R0 resection, *n* (%)

Characteristic	Patients (*n* = 282)	TNM stage					
		IA (*n* = 20, 7.1%)	IB (*n* = 92, 32.6%)	IIA (*n* = 49, 17.4%)	IIB (*n* = 92, 32.6%)	III (*n* = 29, 10.3%)	*P* value
Age (yr)	61 (31-81)	63.5 (50-73)	62 (31-81)	63 (38-78)	59 (31-74)	59 (42-70)	0.076
> 60	136 (48.2)	12 (60.0)	52 (56.5)	31 (63.3)	39 (42.4)	12 (41.4)	
≤ 60	146 (51.8)	8 (40.0)	40 (43.5)	18 (36.7)	53 (57.6)	17 (58.6)	
Sex							0.421
Male	151 (53.5)	7 (35.0)	50 (54.3)	25 (51.0)	51 (55.4)	18 (62.1)	
Female	131 (46.5)	13 (65.0)	42 (45.7)	24 (49.0)	41 (44.6)	11 (37.9)	
Blood type							0.475
A	87 (30.9)	5 (25.0)	26 (28.3)	13 (26.5)	30 (32.6)	13 (44.8)	
B	93 (33.0)	7 (35.0)	34 (37.0)	14 (28.6)	27 (29.3)	11 (37.9)	
AB	22 (7.8)	1 (5.0)	6 (6.5)	4 (8.2)	11 (12.0)	0	
O	80 (28.4)	7 (35.0)	26 (28.3)	18 (36.7)	24 (26.1)	5 (17.2)	
Diabetes							0.816
Absent	201 (71.3)	15 (75.0)	66 (71.7)	33 (67.3)	64 (69.6)	23 (79.3)	
Present	81 (28.7)	5 (25.0)	26 (28.3)	16 (32.7)	28 (30.4)	6 (20.7)	
Smoking status							0.604
Absent	215 (76.2)	13 (65.0)	74 (80.4)	37 (75.5)	68 (73.9)	23 (79.3)	
Present	67 (23.8)	7 (35.0)	18 (19.6)	12 (24.5)	24 (26.1)	6 (20.7)	
Alcohol consumption							0.296
Absent	235 (83.3)	14 (70.0)	78 (84.8)	41 (83.7)	75 (81.5)	27 (93.1)	
Present	47 (16.7)	6 (30.0)	14 (15.2)	8 (16.3)	17 (18.5)	2 (6.9)	
Family history of cancer							0.604
Absent	271 (96.1)	20 (100.0)	88 (95.7)	46 (93.9)	88 (95.7)	29 (100.0)	
Present	11 (3.9)	0	4 (4.3)	3 (6.1)	4 (4.3)	0	
Clinical symptoms							0.021
Absent	57 (20.2)	8 (40.0)	24 (26.1)	7 (14.3)	16 (17.4)	2 (6.9)	
Present	225 (79.8)	12 (60.0)	68 (73.9)	42 (85.7)	76 (82.6)	27 (93.1)	
Open surgery approach							< 0.001
Pancreaticoduodenectomy	130 (46.1)	11 (55.0)	48 (52.2)	10 (20.4)	40 (43.5)	21 (72.4)	
Distal pancreatectomy with splenectomy	152 (53.9)	9 (45.0)	44 (47.8)	39 (79.6)	52 (56.5)	8 (27.6)	
Tumor location							< 0.001
Head and neck	130 (46.1)	11 (55.0)	48 (52.2)	10 (20.4)	40 (43.5)	21 (72.4)	
Body and tail	152 (53.9)	9 (45.0)	44 (47.8)	39 (79.6)	52 (56.5)	8 (27.6)	
Degree of differentiation							0.410
Well	34 (12.1)	0	11 (12.0)	6 (12.2)	13 (14.1)	4 (13.8)	
Moderately	217 (77.0)	16 (80.0)	67 (72.8)	38 (77.6)	73 (79.3)	23 (79.3)	
Poorly	31 (11.0)	4 (20.0)	14 (15.2)	5 (10.2)	6 (6.5)	2 (6.9)	
Lymphovascular invasion							< 0.001
Absent	203 (72.0)	17 (85.0)	73 (79.3)	40 (81.6)	62 (67.4)	11 (37.9)	

Present	79 (28.0)	3 (15.0)	19 (20.7)	9 (18.4)	30 (32.6)	18 (62.1)	
Perineural invasion							0.091
Absent	70 (24.8)	5 (25.0)	25 (27.2)	17 (34.7)	21 (22.8)	2 (6.9)	
Present	212 (75.2)	15 (75.0)	67 (72.8)	32 (65.3)	71 (77.2)	27 (93.1)	
Capsular invasion							0.182
Absent	49 (17.4)	4 (20.0)	18 (19.6)	13 (26.5)	10 (10.9)	4 (13.8)	
Present	233 (82.6)	16 (80.0)	74 (80.4)	36 (73.5)	82 (89.1)	25 (86.2)	
Maximal tumor diameter (cm)							< 0.001
> 4	88 (31.2)	0	1 (1.1)	48 (98.0)	33 (35.9)	6 (20.7)	
≤ 4	194 (68.8)	20 (100.0)	91 (98.9)	1 (2.0)	59 (64.1)	23 (79.3)	
T stage							< 0.001
T1	34 (12.1)	20 (100.0)	0	0	12 (13.0)	2 (6.9)	
T2	159 (56.4)	0	91 (98.9)	0	47 (51.1)	21 (72.4)	
T3	89 (31.6)	0	1 (1.1)	49 (100.0)	33 (35.9)	6 (20.7)	
Lymph node metastasis							< 0.001
Absent	161 (57.1)	20 (100.0)	92 (100.0)	49 (100.0)	0	0	
Present	121 (42.9)	0	0	0	92 (100.0)	29 (100.0)	
N stage							< 0.001
N0	161 (57.1)	20 (100.0)	92 (100.0)	49 (100.0)	0	0	
N1	92 (32.6)	0	0	0	92 (100.0)	0	
N2	29 (10.3)	0	0	0	0	29 (100.0)	
Preoperative CA19-9 level (U/mL)	172.4 (0.6-55412.0)	125.6 (3.4-908.8)	157.0 (0.6-16827.0)	172.4 (1.4-4510.0)	189.5 (12.9-55412.0)	186.2 (29.8-4839.0)	0.158
> 336.4	77 (27.3)	2 (10.0)	21 (22.8)	13 (26.5)	31 (33.7)	10 (34.5)	
≤ 336.4	205 (72.7)	18 (90.0)	71 (77.2)	36 (73.5)	61 (66.3)	19 (65.5)	
Preoperative fibrinogen concentration (g/L)	3.02 (1.20-6.70)	3.21 (1.20-5.00)	3.27 (1.98-6.70)	3.40 (1.83-5.92)	3.13 (2.06-5.53)	3.67 (1.49-5.94)	0.099
> 3.31	141 (50.0)	8 (40.0)	44 (47.8)	30 (61.2)	40 (43.5)	19 (65.5)	
≤ 3.31	141 (50.0)	12 (60.0)	48 (52.2)	19 (38.8)	52 (56.5)	10 (34.5)	
Preoperative D-Dimer concentration (g/L)	0.52 (0.12-582.00)	0.48 (0.16-145.00)	0.52 (0.12-430.00)	0.53 (0.12-582.00)	0.52 (0.16-159.00)	0.54 (0.15-157.00)	0.608
> 0.53	117 (41.5)	8 (40.0)	37 (40.2)	23 (46.9)	34 (37.0)	15 (51.7)	
≤ 0.53	165 (58.5)	12 (60.0)	55 (59.8)	26 (53.1)	58 (63.0)	14 (48.3)	
Adjuvant therapy							0.621
Absent	124 (44.0)	6 (30.0)	42 (45.7)	24 (49.0)	41 (44.6)	11 (37.9)	
Present	158 (56.0)	14 (70.0)	50 (54.3)	25 (51.0)	51 (55.4)	18 (62.1)	

TNM: Tumor, node and metastasis.

fibrinogen concentration > 3.31 g/L was shorter than that of patients with a concentration ≤ 3.31 g/L (Figure 3A).

As shown in Table 3, all patients were grouped into a low-concentration group (≤ 0.53 mg/L) or a high-concentration group (> 0.53 mg/L) based on the optimal cutoff value of the preoperative D-dimer concentration. An increased preoperative D-dimer concentration was significantly correlated with perineural invasion (P = 0.001), maximal tumor diameter (P = 0.027) and the preoperative fibrinogen concentration (P = 0.040). In addition, as presented in the survival curve of the preoperative D-dimer concentration, the OS of patients with a preoperative D-dimer concentration ≤ 0.53 mg/L was relatively shorter than that of patients with a concentration > 0.53 mg/L

Table 2 Correlation between preoperative fibrinogen concentration and clinicopathological characteristics in pancreatic ductal adenocarcinoma patients undergoing radical R0 resection, *n* (%)

Characteristics	Preoperative fibrinogen concentration		*P* value
	> 3.31 g/L (*n* = 141)	≤ 3.31 g/L (*n* = 141)	
Age (yr)			0.812
> 60	72 (25.5)	74 (26.2)	
≤ 60	69 (24.5)	67 (23.8)	
Sex			0.283
Male	71 (25.2)	80 (28.4)	
Female	70 (24.8)	61 (21.6)	
Blood type			0.565
A	39 (13.8)	48 (17.0)	
B	51 (18.1)	42 (14.9)	
AB	10 (3.5)	12 (4.3)	
O	41 (14.5)	39 (13.8)	
Diabetes			0.357
Absent	97 (34.4)	104 (36.9)	
Present	44 (15.6)	37 (13.1)	
Smoking status			0.889
Absent	107 (37.9)	108 (38.3)	
Present	34 (12.1)	33 (11.7)	
Alcohol consumption			0.263
Absent	121 (42.9)	114 (40.4)	
Present	20 (7.1)	27 (9.6)	
Family history of cancer			0.356
Absent	137 (48.6)	134 (47.5)	
Present	4 (1.4)	7 (2.5)	
Clinical symptoms			< 0.001
Absent	15 (5.3)	42 (14.9)	
Present	126 (44.7)	99 (35.1)	
Open surgery approach			< 0.001
Pancreaticoduodenectomy	80 (28.4)	50 (17.7)	
Distal pancreatectomy with splenectomy	61 (21.6)	91 (32.3)	
Tumor location			< 0.001
Head and neck	80 (28.4)	50 (17.7)	
Body and tail	61 (21.6)	91 (32.3)	
Degree of differentiation			0.079
Well	20 (7.1)	14 (5.0)	
Moderately	111 (39.4)	106 (37.6)	
Poorly	10 (3.5)	21 (7.4)	
Lymphovascular invasion			0.233
Absent	97 (34.4)	106 (37.6)	
Present	44 (15.6)	35 (12.4)	

Perineural invasion			0.054
Absent	28 (9.9)	42 (14.9)	
Present	113 (40.1)	99 (35.1)	
Capsular invasion			0.271
Absent	21 (7.4)	28 (9.9)	
Present	120 (42.6)	113 (40.1)	
Maximal tumor diameter (cm)			1.000
> 4	44 (15.6)	44 (15.6)	
≤ 4	97 (34.4)	97 (34.4)	
T stage			0.991
T1	17 (6.0)	17 (6.0)	
T2	80 (28.4)	79 (28.0)	
T3	44 (15.6)	45 (16.0)	
Lymph node metastasis			0.718
Absent	82 (29.1)	79 (28.0)	
Present	59 (20.9)	62 (22.0)	
N stage			0.110
N0	82 (29.1)	79 (28.0)	
N1	40 (14.2)	52 (18.4)	
N2	19 (6.7)	10 (3.5)	
TNM stage			0.099
IA	8 (2.8)	12 (4.3)	
IB	44 (15.6)	48 (17.0)	
IIA	30 (10.6)	19 (6.7)	
IIB	40 (14.2)	52 (18.4)	
III	19 (6.7)	10 (3.5)	
Preoperative CA19-9 level (U/mL)			0.023
> 336.4	47 (16.7)	30 (10.6)	
≤ 336.4	94 (33.3)	111 (39.4)	
Preoperative D-Dimer concentration (g/L)			0.040
> 0.53	67 (23.8)	50 (17.7)	
≤ 0.53	74 (26.2)	91 (32.3)	
Adjuvant therapy			0.631
Absent	64 (22.7)	60 (21.3)	
Present	77 (27.3)	81 (28.7)	

(Figure 3B).

Survival analysis

According to the results of the univariate Cox analysis (Table 4), age (HR: 1.358, 95%CI: 1.036-1.780, $P = 0.027$), clinical symptoms (HR: 0.600, 95%CI: 0.424-0.848, $P = 0.004$), degree of differentiation ($P < 0.001$), capsular invasion (HR: 0.609, 95%CI: 0.420-0.885, $P = 0.009$), maximal tumor diameter (HR: 1.403, 95%CI: 1.058-1.862, $P = 0.019$), T stage ($P = 0.035$), lymph node metastasis (HR: 0.590, 95%CI: 0.449-0.775, $P < 0.001$), N stage ($P = 0.001$), TNM stage ($P = 0.003$), preoperative CA19-9 level (HR: 1.971, 95%CI: 1.469-2.644, $P < 0.001$), preoperative fibrinogen concentration (HR: 1.888, 95%CI: 1.438-2.479, $P < 0.001$), preoperative D-dimer concentration (HR: 1.625, 95%CI: 1.244-2.123, P

Table 3 Correlation between preoperative D-Dimer concentration and clinicopathological characteristics in pancreatic ductal adenocarcinoma patients undergoing radical R0 resection, *n* (%)

Characteristics	Preoperative D-Dimer concentration		*P* value
	> 0.53 mg/L (*n* = 117)	≤ 0.53 mg/L (*n* = 165)	
Age (yr)			0.284
> 60	65 (23.0)	81 (28.7)	
≤ 60	52 (18.4)	84 (29.8)	
Sex			0.260
Male	58 (20.6)	93 (33.0)	
Female	59 (20.9)	72 (25.5)	
Blood type			0.558
A	31 (11.0)	56 (19.9)	
B	40 (14.2)	53 (18.8)	
AB	9 (3.2)	13 (4.6)	
O	37 (13.1)	43 (15.2)	
Diabetes			0.871
Absent	84 (29.8)	117 (41.5)	
Present	33 (11.7)	48 (17.0)	
Smoking status			0.532
Absent	87 (30.9)	128 (45.4)	
Present	30 (10.6)	37 (13.1)	
Alcohol consumption			0.256
Absent	101 (35.8)	134 (47.5)	
Present	16 (5.7)	31 (11.0)	
Family history of cancer			0.785
Absent	112 (39.7)	159 (56.4)	
Present	5 (1.8)	6 (2.1)	
Clinical symptoms			0.845
Absent	23 (8.2)	34 (12.1)	
Present	94 (33.3)	131 (46.5)	
Open surgery approach			0.231
Pancreaticoduodenectomy	49 (17.4)	81 (28.7)	
Distal pancreatectomy with splenectomy	68 (24.1)	84 (29.8)	
Tumor location			0.231
Head and neck	49 (17.3)	81 (28.7)	
Body and tail	68 (24.1)	84 (29.8)	
Degree of differentiation			0.288
Well	18 (6.4)	16 (5.7)	
Moderately	85 (30.1)	132 (46.8)	
Poorly	14 (5.0)	17 (6.0)	
Lymphovascular invasion			0.742
Absent	83 (29.4)	120 (42.6)	
Present	34 (12.1)	45 (16.0)	

Perineural invasion			0.001
Absent	41 (14.5)	29 (10.3)	
Present	76 (27.0)	136 (48.2)	
Capsular invasion			0.831
Absent	21 (7.4)	28 (9.9)	
Present	96 (34.0)	137 (48.6)	
Maximal tumor diameter (cm)			0.027
> 4	45 (16.0)	43 (15.2)	
≤ 4	72 (25.5)	122 (43.3)	
T stage			0.097
T1	14 (5.0)	20 (7.1)	
T2	58 (20.6)	101 (35.8)	
T3	45 (16.0)	44 (15.6)	
Lymph node metastasis			0.769
Absent	68 (24.1)	93 (33.0)	
Present	49 (17.4)	72 (25.5)	
N stage			0.356
N0	68 (24.1)	93 (33.0)	
N1	34 (12.1)	58 (20.6)	
N2	15 (5.3)	14 (5.0)	
TNM stage			0.608
IA	8 (2.8)	12 (4.3)	
IB	37 (13.1)	55 (19.5)	
IIA	23 (8.2)	26 (9.2)	
IIB	34 (12.1)	58 (20.6)	
III	15 (5.3)	14 (5.0)	
Preoperative CA19-9 level (U/mL)			0.056
> 336.4	39 (13.8)	38 (13.5)	
≤ 336.4	78 (27.7)	127 (45.0)	
Preoperative fibrinogen concentration (g/L)			0.040
> 3.31	67 (23.8)	74 (26.2)	
≤ 3.31	50 (17.7)	91 (32.3)	
Adjuvant therapy			0.268
Absent	56 (19.9)	68 (24.1)	
Present	61 (21.6)	97 (34.4)	

< 0.001) and adjuvant therapy (HR: 1.625, 95%CI: 1.244-2.123, P < 0.001) were significantly correlated with the prognosis of PDAC patients undergoing radical R0 resection. However, no obvious significant difference was found in terms of the relationship of sex, blood type, diabetes, smoking status, alcohol consumption, family history of cancer, open surgery approach, tumor location, lymphovascular invasion, or perineural invasion with the OS of PDAC patients undergoing radical R0 resection (P > 0.05).

Furthermore, the multivariate Cox analysis (Table 5) suggested that the degree of differentiation (P < 0.001), capsular invasion (HR: 0.669, 95%CI: 0.456-0.980, P = 0.039), lymph node metastasis (HR: 0.669, 95%CI: 0.502-0.893, P = 0.006), preoperative CA19-9 level (HR: 1.613, 95%CI: 1.187-2.191, P = 0.002), preoperative fibrinogen concentration

Table 4 Univariate analysis for overall survival in pancreatic ductal adenocarcinoma patients undergoing radical R0 resection

Characteristic	HR (95%CI)	*P* value
Age (yr)	1.358 (1.036-1.780)	0.027
> 60		
≤ 60		
Sex	1.281 (0.979-1.675)	0.071
Male		
Female		
Blood type	–	0.579
A		
B		
AB		
O		
Diabetes	0.903 (0.676-1.206)	0.491
Absent		
Present		
Smoking status	0.866 (0.635-1.181)	0.363
Absent		
Present		
Alcohol consumption	1.083 (0.754-1.556)	0.667
Absent		
Present		
Family history of cancer	1.251 (0.617-2.537)	0.535
Absent		
Present		
Clinical symptoms	0.600 (0.424-0.848)	0.004
Absent		
Present		
Open surgery approach	0.954 (0.729-1.249)	0.731
Pancreaticoduodenectomy		
Distal pancreatectomy with splenectomy		
Tumor location	0.954 (0.729-1.249)	0.731
Head and neck		
Body and tail		
Degree of differentiation	–	< 0.001
Well		
Moderately		
Poorly		
Lymphovascular invasion	0.793 (0.590-1.065)	0.123
Absent		
Present		
Perineural invasion	0.905 (0.666-1.231)	0.525
Absent		

Present		
Capsular invasion	0.609 (0.420-0.885)	0.009
Absent		
Present		
Maximal tumor diameter (cm)	1.403 (1.058-1.862)	0.019
> 4		
≤ 4		
T stage	–	0.035
T1		
T2		
T3		
Lymph node metastasis	0.590 (0.449-0.775)	< 0.001
Absent		
Present		
N stage	–	0.001
N0		
N1		
N2		
TNM stage	–	0.003
IA		
IB		
IIA		
IIB		
III		
Preoperative CA19-9 level (U/mL)	1.971 (1.469-2.644)	< 0.001
> 336.4		
≤ 336.4		
Preoperative fibrinogen concentration (g/L)	1.888 (1.438-2.479)	< 0.001
> 3.31		
≤ 3.31		
Preoperative D-Dimer concentration (g/L)	1.625 (1.244-2.123)	< 0.001
> 0.53		
≤ 0.53		
Adjuvant therapy	1.625 (1.244-2.123)	< 0.001
Absent		
Present		

TNM: Tumor, node and metastasis.

(HR: 1.603, 95%CI: 1.201-2.140, P = 0.001), preoperative D-dimer concentration (HR: 1.355, 95%CI: 1.019-1.801, P = 0.036) and adjuvant therapy (HR: 1.620, 95%CI: 1.233-2.128, P = 0.001) were independent prognostic factors for PDAC patients undergoing radical R0 resection.

Synergistic value of fibrinogen combined with D-dimer

It is known that the preoperative fibrinogen concentration and preoperative D-dimer

Table 5 Multivariate analysis for overall survival in pancreatic ductal adenocarcinoma patients undergoing radical R0 resection

Characteristics	HR (95%CI)	Wald	*P* value
Age (yr)	1.285 (0.964-1.713)	2.935	0.087
> 60			
≤ 60			
Degree of differentiation		33.979	< 0.001
Poorly/Well	5.014 (2.737-9.185)	27.240	< 0.001
Moderately/Well	1.667 (1.031-2.696)	4.338	0.037
Capsular invasion	0.669 (0.456-0.980)	4.269	0.039
Absent			
Present			
Lymph node metastasis	0.669 (0.502-0.893)	7.469	0.006
Absent			
Present			
Preoperative CA19-9 level (U/mL)	1.613 (1.187-2.191)	9.340	0.002
> 336.4			
≤ 336.4			
Preoperative fibrinogen concentration (g/L)	1.603 (1.201-2.140)	10.270	0.001
> 3.31			
≤ 3.31			
Preoperative D-Dimer concentration (g/L)	1.355 (1.019-1.801)	4.374	0.036
> 0.53			
≤ 0.53			
Adjuvant therapy	1.620 (1.233-2.128)	11.983	0.001
Absent			
Present			

concentration are independent prognostic factors for PDAC patients undergoing radical R0 resection. Our study aimed to further explore their synergistic value in predicting the OS of these patients. Based on the optimal cutoff values of the preoperative fibrinogen concentration and preoperative D-dimer concentration, the survival curves of the four different groups of patients were preliminarily compared, and a significant difference in OS was observed between the four groups ($P < 0.001$) (Figure 4A). Notably, patients with high concentrations of fibrinogen and/or D-dimer had similar survival conditions, and thus, these patients were integrated into one group. As a result, the enrolled patients were redivided into an any-high group (n = 191, 67.7%) and a low-low group (n = 91, 32.3%). Table 6 shows the correlations between the clinicopathological characteristics of the enrolled patients with OS. The median OS duration of the two groups was 15.43 mo (any-high group) and 31.17 mo (low-low group), with a significant difference in OS between the groups ($P < 0.001$) (Figure 4B). Furthermore, the indicator of preoperative fibrinogen combined with D-dimer was included in the multivariate Cox regression analysis. We found that the degree of differentiation ($P < 0.001$), lymph node metastasis (HR: 0.663, 95%CI: 0.497-0.883, $P = 0.005$), preoperative CA19-9 level (HR: 1.699, 95%CI: 1.258-2.293, $P = 0.001$), adjuvant therapy (HR: 1.582, 95%CI: 1.202-2.081, $P = 0.001$) and preoperative combined grouping (HR: 2.397, 95%CI: 1.723-3.335, $P < 0.001$) were independent prognostic factors of OS in PDAC patients undergoing radical R0 resection (Table 7). Patients with low concentrations of preoperative fibrinogen and D-dimer had a satisfactory prognosis.

Table 6 Correlation between preoperative combined groups and clinicopathological characteristics in pancreatic ductal adenocarcinoma patients undergoing radical R0 resection, *n* (%)

Characteristics	Preoperative combined groups		*P* value
	Any-high group (*n* = 191)	Low-low group (*n* = 91)	
Age (yr)			0.590
> 60	101 (35.8)	45 (16.0)	
≤ 60	90 (31.9)	46 (16.3)	
Sex			0.562
Male	100 (35.5)	51 (18.1)	
Female	91 (32.3)	40 (14.2)	
Blood type			0.480
A	54 (19.1)	33 (11.7)	
B	65 (23.0)	28 (9.9)	
AB	14 (5.0)	8 (2.8)	
O	58 (20.6)	22 (7.8)	
Diabetes			0.969
Absent	136 (48.2)	65 (23.0)	
Present	55 (19.5)	26 (9.2)	
Smoking status			0.433
Absent	143 (50.7)	72 (25.5)	
Present	48 (17.0)	19 (6.7)	
Alcohol consumption			0.531
Absent	161 (57.1)	74 (26.2)	
Present	30 (10.6)	17 (6.0)	
Family history of cancer			0.767
Absent	184 (65.2)	87 (30.9)	
Present	7 (2.5)	4 (1.4)	
Clinical symptoms			0.002
Absent	29 (10.3)	28 (9.9)	
Present	162 (57.4)	63 (22.3)	
Open surgery approach			0.128
Pancreaticoduodenectomy	94 (33.3)	36 (12.8)	
Distal pancreatectomy with splenectomy	97 (34.4)	55 (19.5)	
Tumor location			0.128
Head and neck	94 (33.3)	36 (12.8)	
Body and tail	97 (34.4)	55 (19.5)	
Degree of differentiation			0.392
Well	25 (8.9)	9 (3.2)	
Moderately	148 (52.5)	69 (24.5)	
Poorly	18 (6.4)	13 (4.6)	
Lymphovascular invasion			0.322
Absent	134 (47.5)	69 (24.5)	
Present	57 (20.2)	22 (7.8)	

Perineural invasion			0.290
Absent	51 (18.1)	19 (6.7)	
Present	140 (49.6)	72 (25.5)	
Capsular invasion			0.159
Absent	29 (10.3)	20 (7.1)	
Present	162 (57.4)	71 (25.2)	
Maximal tumor diameter (cm)			0.021
> 4	68 (24.1)	20 (7.1)	
≤ 4	123 (43.6)	71 (25.2)	
T stage			0.048
T1	23 (8.2)	11 (3.9)	
T2	99 (35.1)	60 (21.3)	
T3	69 (24.5)	20 (7.1)	
Lymph node metastasis			0.615
Absent	111 (39.4)	50 (17.7)	
Present	80 (28.4)	41 (14.5)	
N stage			0.026
N0	111 (39.4)	50 (17.7)	
N1	55 (19.5)	37 (13.1)	
N2	25 (8.9)	4 (1.4)	
TNM stage			0.002
IA	13 (4.6)	7 (2.5)	
IB	56 (19.9)	36 (12.8)	
IIA	42 (14.9)	7 (2.5)	
IIB	55 (19.5)	37 (13.1)	
III	25 (8.9)	4 (1.4)	
Preoperative CA19-9 level (U/mL)			0.095
> 336.4	58 (20.6)	19 (6.7)	
≤ 336.4	133 (47.2)	72 (25.5)	
Adjuvant therapy			0.198
Absent	89 (31.6)	35 (12.4)	
Present	102 (36.2)	56 (19.9)	

The any-high group for preoperative fibrinogen concentration > 3.31 g/L and/or preoperative D-dimer concentration > 0.53 mg/L group; the low-low group for preoperative fibrinogen concentration ≤ 3.31 g/L and preoperative D-dimer concentration ≤ 0.53 mg/L group. TNM: Tumor, node and metastasis.

DISCUSSION

In our study, it was found that both a high preoperative fibrinogen concentration (> 3.31 g/L, $P = 0.001$) and a high preoperative D-dimer concentration (> 0.53 mg/L, $P = 0.036$) were associated with short OS in PDAC patients undergoing radical R0 resection. To further explore the synergistic value of preoperative fibrinogen and D-dimer, the two indicators were combined and included in a multivariate analysis. Consequently, patients in the low-low group (preoperative fibrinogen concentration ≤ 3.31 g/L and preoperative D-dimer concentration ≤ 0.53 mg/L) had a prolonged median OS, and those in the any-high group (preoperative fibrinogen concentration > 3.31 g/L and/or preoperative D-dimer concentration > 0.53 mg/L) had a poorer prognosis (any-high group *vs* low-low group, HR: 2.397, 95%CI: 1.723-3.335, $P < 0.001$).

Table 7 Univariate and multivariate analysis for overall survival in pancreatic ductal adenocarcinoma patients undergoing radical R0 resection according to the combination of preoperative fibrinogen and D-dimer

Characteristics	HR (95%CI)	Wald	*P* value	MOS (mo)
Univariate analysis				
Preoperative combined grouping	2.500 (1.806-3.462)	–	0.000	
Any-high group				15.43
Low-low group				31.17
Multivariate analysis				
Age (year)	1.308 (0.985-1.736)	3.447	0.063	
> 60				16.73
≤ 60				18.67
Degree of differentiation		36.927	0.000	
Poorly/well	5.267 (2.871-9.663)	28.794	0.000	8.07 *vs* 51.77
Moderately/well	1.631 (1.011-2.633)	4.012	0.045	18.40 *vs* 51.77
Capsular invasion	0.691 (0.471-1.013)	3.579	0.059	
Absent				24.00
Present				16.73
Lymph node metastasis	0.663 (0.497-0.883)	7.882	0.005	
Absent				19.90
Present				15.03
Preoperative CA19-9 level (U/mL)	1.699 (1.258-2.293)	11.960	0.001	
> 336.4				12.23
≤ 336.4				19.90
Adjuvant therapy	1.582 (1.202-2.081)	10.731	0.001	
Absent				14.17
Present				20.37
Preoperative combined grouping	2.397 (1.723-3.335)	26.908	0.000	
Any-high group				15.43
Low-low group				31.17

The any-high group for preoperative fibrinogen concentration > 3.31 g/L and/or preoperative D-dimer concentration > 0.53 mg/L group; the low-low group for preoperative fibrinogen concentration ≤ 3.31 g/L and preoperative D-dimer concentration ≤ 0.53 mg/L group. MOS: Median overall survival.

To the best of our knowledge, this is the first report on the role of preoperative fibrinogen combined with D-dimer in predicting OS in PDAC patients undergoing radical R0 resection.

It is known that almost all patients with malignant tumors are in a hypercoagulable state[13]. It has been confirmed that tumor progression exhibits an intimate association with the hyperactivity of the coagulation system and secondary increased fibrinolytic activity[21]. VTE is a common complication of patients with cancer, and cancer-associated VTE is the second leading cause of death in these patients[15,16]. The incidence of VTE in patients with PC is particularly high, reaching 36%[17]. D-dimer has been documented to possess high sensitivity in the diagnosis of VTE, deep venous thrombosis, pulmonary embolism and disseminated intravascular coagulation. Nevertheless, prior studies have reported an increase in the D-dimer concentration in pregnant women and patients with tumors or infectious diseases[26]. D-dimer, named because D-dimer contains the protein D fragments of two fibrins linked by cross-linking, is one of the fibrin degradation products (FDPs) produced by the sequential effect of thrombin, factor XIIIa and plasmin[20]. D-dimer is a specific FDP with the simplest structure, and its increase in concentration may indicate the existence of a

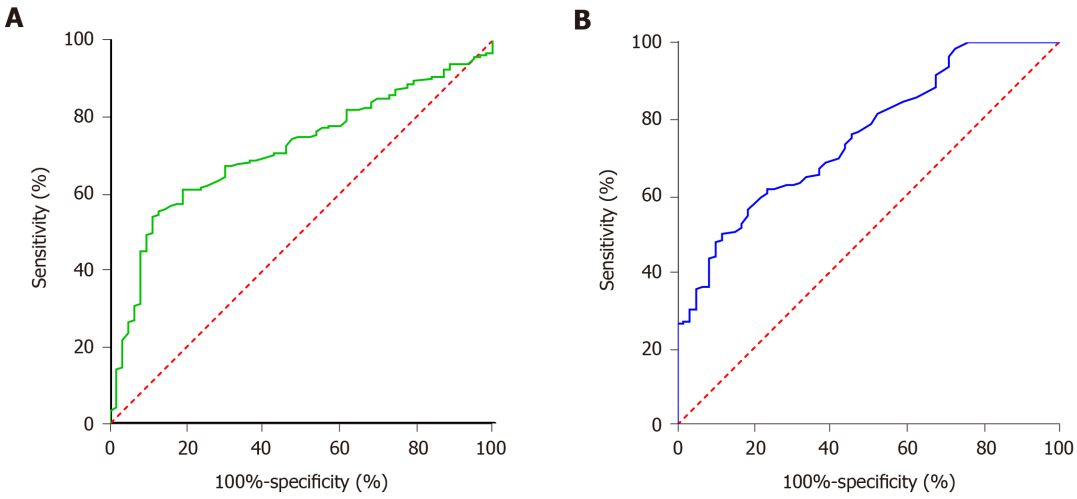

Figure 2 Receiver operating characteristic curve for overall survival analysis according to the preoperative fibrinogen concentration and preoperative D-dimer concentration. A: The area under the receiver operating characteristic (ROC) curve (AUC) was calculated to show the diagnostic ability of preoperative fibrinogen. In this model, the optimal cutoff value of the preoperative fibrinogen concentration was 3.31 g/L, and the AUC was 0.714 (95%CI: 0.649-0.779), while the sensitivity and specificity at the maximal Youden's index were 61.14% and 79.37%, respectively; B: The optimal cutoff value of the preoperative D-dimer concentration was 0.52 mg/L, and the AUC was 0.753 (95%CI: 0.687-0.819), while the sensitivity and specificity at the maximal Youden's index were 58.78% and 78.82%, respectively.

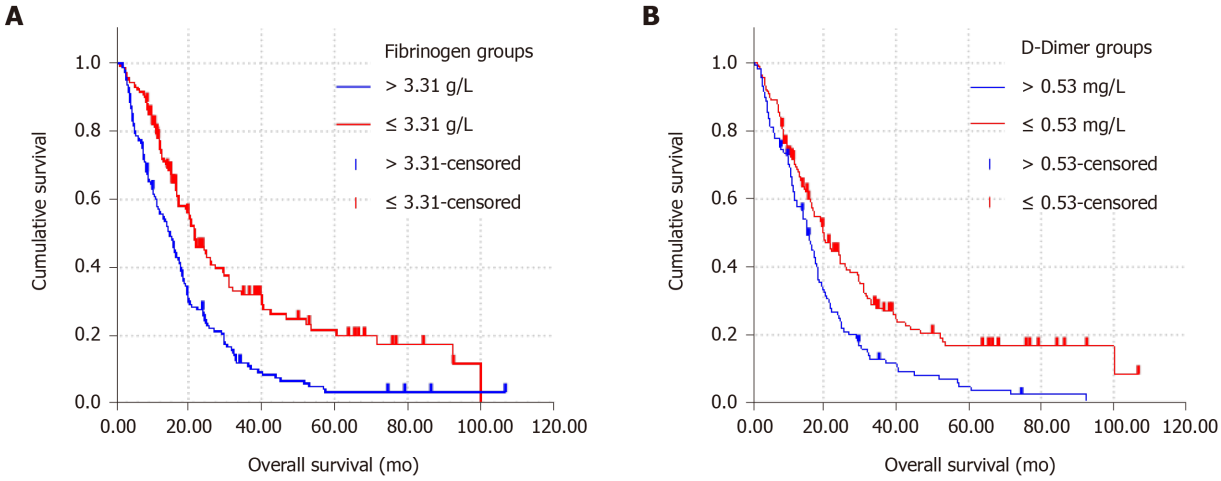

Figure 3 Kaplan-Meier curves were generated based on the optimal cutoff values of the preoperative fibrinogen concentration and preoperative D-dimer concentration. A: Comparison between the preoperative fibrinogen low-concentration group (red line: ≤ 3.31 g/L) and the preoperative fibrinogen high-concentration group (blue line: > 3.31 g/L) ($P < 0.05$); B: Comparison between the preoperative D-dimer low-concentration group (red line: ≤ 0.53 mg/L) and the preoperative D-dimer high-concentration group (blue line: > 0.53 mg/L) ($P < 0.05$).

hypercoagulable state and secondary increased fibrinolytic activity[20]. Accumulating evidence has shown that a high D-dimer concentration is associated with an increased risk of death in patients with malignant tumors[23], such as non-small cell lung cancer[27], breast cancer[28,29], gastric cancer[30], cervical cancer[31] and ovarian cancer[32]. Moreover, it has been reported that an increase in the D-dimer concentration is an important marker of early tumor metastasis in operable breast cancer patients[33]. D-dimer can predict not only the prognosis of patients with PC[34], but also the unresectability of this cancer (positive *vs* negative predictive value; 89%, 95%CI: 77%-96% *vs* 48%, 95%CI: 33%-63%)[35].

For years, D-dimer has been the focus of investigations on the mechanism of cancer-associated coagulation disorders. However, the role of fibrinogen has been ignored compared with that of D-dimer. Specifically, fibrinogen is a soluble glycoprotein composed of three different polypeptide chains (Aα, Bβ and γ) and is normally synthesized by the liver and released into the blood[36]. In brief, the coagulation process involving fibrinogen is the process by which soluble fibrinogen develops into insoluble fibrin and ultimately forms a blood clot. In addition, fibrinogen participates

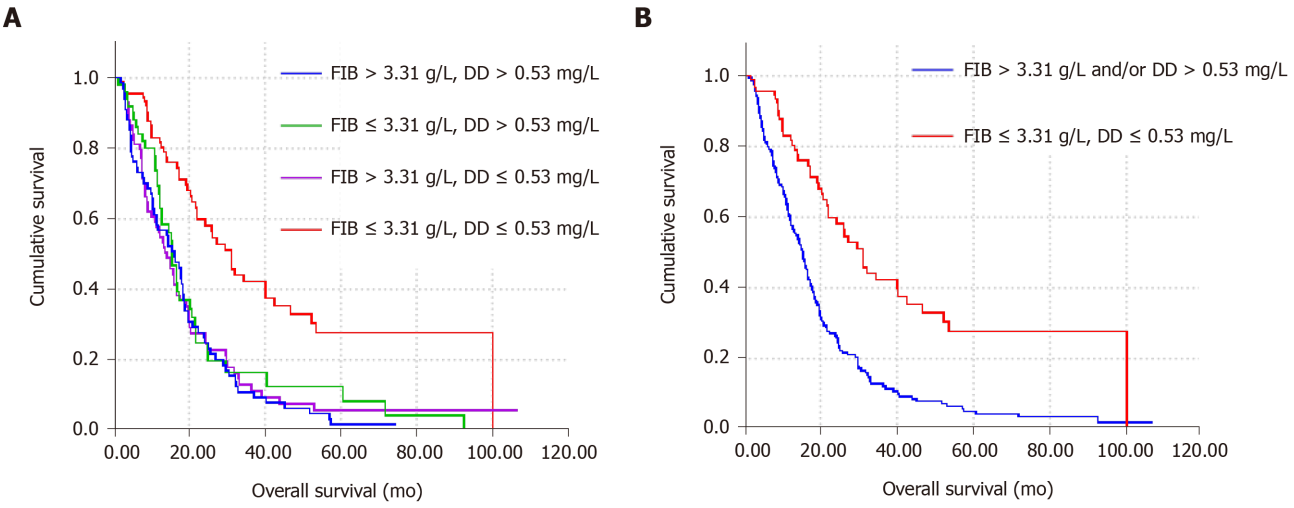

Figure 4 Difference in survival between groups based on preoperative fibrinogen combined with D-dimer indicated by Kaplan-Meier curves. A: Preliminary analysis after subdividing the four groups of enrolled patients (blue line: preoperative fibrinogen concentration > 3.31 g/L and preoperative D-dimer concentration > 0.53 mg/L; green line: preoperative D-dimer concentration > 0.53 mg/L and preoperative fibrinogen concentration ≤ 3.31 g/L; purple line: preoperative fibrinogen concentration > 3.31 g/L and preoperative D-dimer concentration ≤ 0.53 mg/L; and red line: preoperative fibrinogen concentration ≤ 3.31 g/L and preoperative D-dimer concentration ≤ 0.53 mg/L); B: Subgroup analysis of enrolled patients (blue line: preoperative fibrinogen concentration > 3.31 g/L and/or preoperative D-dimer concentration > 0.53 mg/L; and red line: preoperative fibrinogen concentration ≤ 3.31 g/L and preoperative D-dimer concentration ≤ 0.53 mg/L). FIB: Fibrinogen; DD: D-dimer.

in the systemic inflammatory response as an acute inflammatory protein[18], and the latter is a key factor in the occurrence and development of many malignant tumors, including PC[19,37,38].

Angiogenesis can be stimulated by the protein hydrolysate produced by fibrinogen during coagulation, which plays an essential role in tumor growth and metastasis[39]. Fibrinogen can also promote the adhesion of platelets to tumor cells, and their synergistic effect can further protect tumor cells from natural killer cells[40]. Moreover, fibrinogen can bind directly to growth factors that function significantly in angiogenesis, tumor proliferation and metastasis[41-43], such as vascular endothelial growth factor, the fibroblast growth factor family and transforming growth factor-β. Furthermore, epithelial-mesenchymal transition (EMT) is the basis of embryonic development and can promote the invasion and spread of tumors by malignant epithelial cells. It has been reported that EMT exhibits an intimate association with the early metastasis and high invasiveness of PC[44,45]. It is important to note that fibrinogen can further enhance the invasion and metastasis of tumor cells through EMT[46,47]. Recent clinical studies have documented that the fibrinogen concentration is negatively correlated with the prognosis of solid malignancies[22], such as head and neck cancer[48], non-small cell lung cancer[49], gallbladder cancer[46], and urinary system tumors[50], and can predict distant metastasis[51]. The preoperative fibrinogen concentration showed a positive correlation with the stage of PC[52]. In addition, a high fibrinogen concentration can predict a poor prognosis in patients with advanced PC (HR 2.184, 95%CI: 1.574-3.032, $P < 0.001$)[53].

Both fibrinogen and D-dimer are common indicators with critical value in the coagulation/fibrinolysis system. Our study revealed that the median OS duration of the low-low group was much longer than that of the any-high group. This result suggests that preoperative treatment by reducing the plasma concentrations of fibrinogen and D-dimer may have a beneficial effect on the prognosis of PDAC patients undergoing radical R0 resection. As evidenced by multiple clinical studies, anticoagulant therapy with low-molecular-weight heparin can delay cancer progression[54-56], and vitamin K antagonists play a protective role in cancer patients[57]. However, it should be noted that the aforementioned treatments increase the risk of bleeding, especially for perioperative patients who undergo pancreaticoduodenectomy. Anticoagulant therapy should be emphasized throughout the treatment process. Additionally, the occurrence of thrombotic events is related to the presence of chronic underlying diseases[58], surgical approaches and the duration[59], and toxicity of chemotherapy[60].

Hypercoagulability in PC patients is a consequence of the combined action of the coagulation-promoting factors of tumor cells themselves and their microenviron-

ment[61]. Cancer patients have an activated coagulation/fibrinolysis system with inflammatory involvement. Therefore, the functional inhibition of fibrinogen and D-dimer *in vivo* may provide new insight into the treatment of PC. This inspired us to screen new drug targets to prevent and treat thrombosis without affecting hemostasis, thereby improving the survival of patients with PC.

However, there are some limitations to this study. This was a single-center retrospective study, and a multicenter prospective study with a larger sample size is required to verify these results. In addition, our study focused merely on the role of preoperative fibrinogen and D-dimer. In the future, statistical analysis of postoperative concentrations with the inclusion of more coagulation-related indicators will be carried out to analyze their dynamic changes over disease progression, and the results may be more instructive.

CONCLUSION

Our study reports for the first time the synergistic value of preoperative fibrinogen and D-dimer in evaluating the prognosis of PDAC patients undergoing radical R0 resection. The detection of fibrinogen and D-dimer is included in preoperative routine blood tests within most hospitals at present, with high accessibility in the clinical setting. The OS of these patients can be roughly predicted according to the test results. Low concentrations of fibrinogen and D-dimer may indicate a satisfactory prognosis. However, the findings of our study also suggest that it is necessary to explore the feasibility of preoperative anticoagulant therapy to carry out intervention treatment in the early disease stage to ultimately improve patient prognosis.

ARTICLE HIGHLIGHTS

Research background

Pancreatic cancer (PC) is one of the digestive system tumors with the highest degree of malignancy and the worst prognosis. Patients with malignant tumors frequently exhibit hyperactivation of the coagulation system and secondary increased fibrinolytic activity. Fibrinogen and D-dimer are common indicators that are crucial in the coagulation/fibrinolysis system.

Research motivation

Both indicators, fibrinogen and D-dimer, have been verified to have predictive value in the overall survival (OS) of many patients with solid malignancies. To date, there have been no reports on the correlation of the synergistic value of fibrinogen and D-dimer with the prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) undergoing radical R0 resection.

Research objectives

The main objective of our study was to explore the prognostic significance of fibrinogen combined with D-dimer in PDAC patients undergoing radical R0 resection.

Research methods

We retrospectively analyzed the data of 282 PDAC patients undergoing radical R0 resection in the Cancer Hospital, Chinese Academy of Medical Sciences, between January 2010 and December 2019. The surv_cutpoint function of R language was used to determine the optimal cutoff values of the preoperative fibrinogen concentration and preoperative D-dimer concentration. Enrolled patients were further divided into the any-high group (high preoperative fibrinogen concentration and/or high preoperative D-dimer concentration) and the low-low group (low preoperative fibrinogen and D-dimer concentrations) according to the optimal cutoff values.

Research results

The optimal cutoff values of the preoperative fibrinogen concentration and preoperative D-dimer concentration were 3.31 g/L and 0.53 mg/L, respectively. Multivariate Cox regression analysis showed that the preoperative fibrinogen concentration (HR: 1.603, 95%CI: 1.201-2.140, P = 0.001) and preoperative D-dimer concentration (HR: 1.355, 95%CI: 1.019-1.801, P = 0.036) exhibited obvious correlations

with the OS of PDAC patients undergoing radical R0 resection. A prognostic analysis was further performed based on the subgroup results by using fibrinogen combined with D-dimer. The median OS duration of the low-low group (31.17 mo) was significantly longer than that of the any-high group (15.43 mo).

Research conclusions

Preoperative fibrinogen combined with D-dimer plays a predictive role in OS, and low preoperative fibrinogen and D-dimer concentrations can indicate prolonged OS in PDAC patients undergoing radical R0 resection.

Research perspectives

In the future, multicenter prospective studies with a larger sample size are required to verify our results. The inclusion of more coagulation-related indicators should be carried out to analyze their dynamic changes over disease progression, and the results may be more instructive.

REFERENCES

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34 [PMID: 30620402 DOI: 10.3322/caac.21551]

2 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

3 **Howlader N**, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review, 1975-2017, National Cancer Institute, based on November 2019 SEER data submission, posted to the SEER web site, April 2020, [cited 2020-09-20] Available from: https://seer.cancer.gov/csr/1975_2017/browse_csr.php?sectionSEL=22&pageSEL=sect_22_table.08

4 **Rahib L**, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014; **74**: 2913-2921 [PMID: 24840647 DOI: 10.1158/0008-5472.CAN-14-0155]

5 **Kamisawa T**, Wood LD, Itoi T, Takaori K. Pancreatic cancer. *Lancet* 2016; **388**: 73-85 [PMID: 26830752 DOI: 10.1016/S0140-6736(16)00141-0]

6 **Grossberg AJ**, Chu LC, Deig CR, Fishman EK, Hwang WL, Maitra A, Marks DL, Mehta A, Nabavizadeh N, Simeone DM, Weekes CD, Thomas CR Jr. Multidisciplinary standards of care and recent progress in pancreatic ductal adenocarcinoma. *CA Cancer J Clin* 2020; **70**: 375-403 [PMID: 32683683 DOI: 10.3322/caac.21626]

7 **Hoem D**, Viste A. Improving survival following surgery for pancreatic ductal adenocarcinoma--a ten-year experience. *Eur J Surg Oncol* 2012; **38**: 245-251 [PMID: 22217907 DOI: 10.1016/j.ejso.2011.12.010]

8 **Kulemann B**, Hoeppner J, Wittel U, Glatz T, Keck T, Wellner UF, Bronsert P, Sick O, Hopt UT, Makowiec F, Riediger H. Perioperative and long-term outcome after standard pancreaticoduodenectomy, additional portal vein and multivisceral resection for pancreatic head cancer. *J Gastrointest Surg* 2015; **19**: 438-444 [PMID: 25567663 DOI: 10.1007/s11605-014-2725-8]

9 **Bond-Smith G**, Banga N, Hammond TM, Imber CJ. Pancreatic adenocarcinoma. *BMJ* 2012; **344**: e2476 [PMID: 22592847 DOI: 10.1136/bmj.e2476]

10 **Wolfgang CL**, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, Hruban RH. Recent progress in pancreatic cancer. *CA Cancer J Clin* 2013; **63**: 318-348 [PMID: 23856911 DOI: 10.3322/caac.21190]

11 **Groot VP**, Gemenetzis G, Blair AB, Rivero-Soto RJ, Yu J, Javed AA, Burkhart RA, Rinkes IHMB, Molenaar IQ, Cameron JL, Weiss MJ, Wolfgang CL, He J. Defining and Predicting Early Recurrence in 957 Patients With Resected Pancreatic Ductal Adenocarcinoma. *Ann Surg* 2019; **269**: 1154-1162 [PMID: 31082915 DOI: 10.1097/SLA.0000000000002734]

12 **Gillen S**, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010; **7**: e1000267 [PMID: 20422030 DOI: 10.1371/journal.pmed.1000267]

13 **Lee AY**. Cancer and thromboembolic disease: pathogenic mechanisms. *Cancer Treat Rev* 2002; **28**: 137-140 [PMID: 12234564 DOI: 10.1016/s0305-7372(02)00044-0]

14 **Iguchi T**, Sugimachi K, Mano Y, Kono M, Kagawa M, Nakanoko T, Uehara H, Sugiyama M, Ota M, Ikebe M, Morita M, Toh Y. The Preoperative Prognostic Nutritional Index Predicts the Development of Deep Venous Thrombosis After Pancreatic Surgery. *Anticancer Res* 2020; **40**: 2297-2301 [PMID: 32234929 DOI: 10.21873/anticanres.14195]

15 **Prandoni P**, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, Girolami A. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; **100**:

3484-3488 [PMID: 12393647 DOI: 10.1182/blood-2002-01-0108]
16 **Khorana AA**, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007; **5**: 632-634 [PMID: 17319909 DOI: 10.1111/j.1538-7836.2007.02374.x]
17 **Epstein AS**, Soff GA, Capanu M, Crosbie C, Shah MA, Kelsen DP, Denton B, Gardos S, O'Reilly EM. Analysis of incidence and clinical outcomes in patients with thromboembolic events and invasive exocrine pancreatic cancer. *Cancer* 2012; **118**: 3053-3061 [PMID: 21989534 DOI: 10.1002/cncr.26600]
18 **Trinchieri G**. Cancer Immunity: Lessons From Infectious Diseases. *J Infect Dis* 2015; **212** Suppl 1: S67-S73 [PMID: 26116736 DOI: 10.1093/infdis/jiv070]
19 **Mantovani A**. Cancer: Inflaming metastasis. *Nature* 2009; **457**: 36-37 [PMID: 19122629 DOI: 10.1038/457036b]
20 **Adam SS**, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. *Blood* 2009; **113**: 2878-2887 [PMID: 19008457 DOI: 10.1182/blood-2008-06-165845]
21 **Satoh T**, Matsumoto K, Tanaka YO, Akiyama A, Nakao S, Sakurai M, Ochi H, Onuki M, Minaguchi T, Sakurai H, Yoshikawa H. Incidence of venous thromboembolism before treatment in cervical cancer and the impact of management on venous thromboembolism after commencement of treatment. *Thromb Res* 2013; **131**: e127-e132 [PMID: 23433998 DOI: 10.1016/j.thromres.2013.01.027]
22 **Perisanidis C**, Psyrri A, Cohen EE, Engelmann J, Heinze G, Perisanidis B, Stift A, Filipits M, Kornek G, Nkenke E. Prognostic role of pretreatment plasma fibrinogen in patients with solid tumors: A systematic review and meta-analysis. *Cancer Treat Rev* 2015; **41**: 960-970 [PMID: 26604093 DOI: 10.1016/j.ctrv.2015.10.002]
23 **Ay C**, Dunkler D, Pirker R, Thaler J, Quehenberger P, Wagner O, Zielinski C, Pabinger I. High D-dimer levels are associated with poor prognosis in cancer patients. *Haematologica* 2012; **97**: 1158-1164 [PMID: 22371182 DOI: 10.3324/haematol.2011.054718]
24 **Liu Z**, Guo H, Gao F, Shan Q, Li J, Xie H, Zhou L, Xu X, Zheng S. Fibrinogen and D-dimer levels elevate in advanced hepatocellular carcinoma: High pretreatment fibrinogen levels predict poor outcomes. *Hepatol Res* 2017; **47**: 1108-1117 [PMID: 27914119 DOI: 10.1111/hepr.12848]
25 **Bockhorn M**, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, Asbun HJ, Bassi C, Büchler M, Charnley RM, Conlon K, Cruz LF, Dervenis C, Fingerhutt A, Friess H, Gouma DJ, Hartwig W, Lillemoe KD, Montorsi M, Neoptolemos JP, Shrikhande SV, Takaori K, Traverso W, Vashist YK, Vollmer C, Yeo CJ, Izbicki JR; International Study Group of Pancreatic Surgery. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014; **155**: 977-988 [PMID: 24856119 DOI: 10.1016/j.surg.2014.02.001]
26 **Kabrhel C**, Mark Courtney D, Camargo CA Jr, Plewa MC, Nordenholz KE, Moore CL, Richman PB, Smithline HA, Beam DM, Kline JA. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. *Acad Emerg Med* 2010; **17**: 589-597 [PMID: 20624138 DOI: 10.1111/j.1553-2712.2010.00765.x]
27 **Shiina Y**, Nakajima T, Yamamoto T, Tanaka K, Sakairi Y, Wada H, Suzuki H, Yoshino I. The D-dimer level predicts the postoperative prognosis in patients with non-small cell lung cancer. *PLoS One* 2019; **14**: e0222050 [PMID: 31877562 DOI: 10.1371/journal.pone.0222050]
28 **Dirix LY**, Salgado R, Weytjens R, Colpaert C, Benoy I, Huget P, van Dam P, Prové A, Lemmens J, Vermeulen P. Plasma fibrin D-dimer levels correlate with tumour volume, progression rate and survival in patients with metastatic breast cancer. *Br J Cancer* 2002; **86**: 389-395 [PMID: 11875705 DOI: 10.1038/sj.bjc.6600069]
29 **Batschauer APB**, Figueiredo CP, Bueno EC, Ribeiro MA, Dusse LMS, Fernandes AP, Gomes KB, Carvalho MG. D-dimer as a possible prognostic marker of operable hormone receptor-negative breast cancer. *Ann Oncol* 2010; **21**: 1267-1272 [PMID: 19880435 DOI: 10.1093/annonc/mdp474]
30 **Tas F**, Ciftci R, Kilic L, Serilmez M, Karabulut S, Duranyildiz D. Clinical and prognostic significance of coagulation assays in gastric cancer. *J Gastrointest Cancer* 2013; **44**: 285-292 [PMID: 23536321 DOI: 10.1007/s12029-013-9490-x]
31 **Luo YL**, Chi PD, Zheng X, Zhang L, Wang XP, Chen H. Preoperative D-dimers as an independent prognostic marker in cervical carcinoma. *Tumour Biol* 2015; **36**: 8903-8911 [PMID: 26071675 DOI: 10.1007/s13277-015-3650-5]
32 **Yamada Y**, Kawaguchi R, Iwai K, Niiro E, Morioka S, Tanase Y, Kobayashi H. Preoperative plasma D-dimer level is a useful prognostic marker in ovarian cancer. *J Obstet Gynaecol* 2020; **40**: 102-106 [PMID: 31335252 DOI: 10.1080/01443615.2019.1606176]
33 **Blackwell K**, Haroon Z, Broadwater G, Berry D, Harris L, Iglehart JD, Dewhirst M, Greenberg C. Plasma D-dimer levels in operable breast cancer patients correlate with clinical stage and axillary lymph node status. *J Clin Oncol* 2000; **18**: 600-608 [PMID: 10653875 DOI: 10.1200/JCO.2000.18.3.600]
34 **Liu P**, Zhu Y, Liu L. Elevated pretreatment plasma D-dimer levels and platelet counts predict poor prognosis in pancreatic adenocarcinoma. *Onco Targets Ther* 2015; **8**: 1335-1340 [PMID: 26082650 DOI: 10.2147/OTT.S82329]
35 **Stender MT**, Larsen AC, Sall M, Thorlacius-Ussing O. D-Dimer predicts prognosis and non-resectability in patients with pancreatic cancer: a prospective cohort study. *Blood Coagul Fibrinolysis* 2016; **27**: 597-601 [PMID: 27182687 DOI: 10.1097/MBC.0000000000000559]

36 **Adams RA**, Schachtrup C, Davalos D, Tsigelny I, Akassoglou K. Fibrinogen signal transduction as a mediator and therapeutic target in inflammation: lessons from multiple sclerosis. *Curr Med Chem* 2007; **14**: 2925-2936 [PMID: 18045138 DOI: 10.2174/092986707782360015]

37 **Coussens LM**, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860-867 [PMID: 12490959 DOI: 10.1038/nature01322]

38 **Grivennikov SI**, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; **140**: 883-899 [PMID: 20303878 DOI: 10.1016/j.cell.2010.01.025]

39 **Zhao C**, Su Y, Zhang J, Feng Q, Qu L, Wang L, Liu C, Jiang B, Meng L, Shou C. Fibrinogen-derived fibrinostatin inhibits tumor growth through anti-angiogenesis. *Cancer Sci* 2015; **106**: 1596-1606 [PMID: 26300396 DOI: 10.1111/cas.12797]

40 **Zheng S**, Shen J, Jiao Y, Liu Y, Zhang C, Wei M, Hao S, Zeng X. Platelets and fibrinogen facilitate each other in protecting tumor cells from natural killer cytotoxicity. *Cancer Sci* 2009; **100**: 859-865 [PMID: 19302289 DOI: 10.1111/j.1349-7006.2009.01115.x]

41 **Staton CA**, Brown NJ, Lewis CE. The role of fibrinogen and related fragments in tumour angiogenesis and metastasis. *Expert Opin Biol Ther* 2003; **3**: 1105-1120 [PMID: 14519075 DOI: 10.1517/14712598.3.7.1105]

42 **Witsch E**, Sela M, Yarden Y. Roles for growth factors in cancer progression. *Physiology (Bethesda)* 2010; **25**: 85-101 [PMID: 20430953 DOI: 10.1152/physiol.00045.2009]

43 **Martino MM**, Briquez PS, Ranga A, Lutolf MP, Hubbell JA. Heparin-binding domain of fibrin(ogen) binds growth factors and promotes tissue repair when incorporated within a synthetic matrix. *Proc Natl Acad Sci USA* 2013; **110**: 4563-4568 [PMID: 23487783 DOI: 10.1073/pnas.1221602110]

44 **von Burstin J**, Eser S, Paul MC, Seidler B, Brandl M, Messer M, von Werder A, Schmidt A, Mages J, Pagel P, Schnieke A, Schmid RM, Schneider G, Saur D. E-cadherin regulates metastasis of pancreatic cancer *in vivo* and is suppressed by a SNAIL/HDAC1/HDAC2 repressor complex. *Gastroenterology* 2009; **137**: 361-371, 371.e1-371. e5 [PMID: 19362090 DOI: 10.1053/j.gastro.2009.04.004]

45 **Ikenaga N**, Ohuchida K, Mizumoto K, Akagawa S, Fujiwara K, Eguchi D, Kozono S, Ohtsuka T, Takahata S, Tanaka M. Pancreatic cancer cells enhance the ability of collagen internalization during epithelial-mesenchymal transition. *PLoS One* 2012; **7**: e40434 [PMID: 22792318 DOI: 10.1371/journal.pone.0040434]

46 **Shu YJ**, Weng H, Bao RF, Wu XS, Ding Q, Cao Y, Wang XA, Zhang F, Xiang SS, Li HF, Li ML, Mu JS, Wu WG, Liu YB. Clinical and prognostic significance of preoperative plasma hyperfibrinogenemia in gallbladder cancer patients following surgical resection: a retrospective and *in vitro* study. *BMC Cancer* 2014; **14**: 566 [PMID: 25096189 DOI: 10.1186/1471-2407-14-566]

47 **Zhang X**, Wang F, Huang Y, Ke K, Zhao B, Chen L, Liao N, Wang L, Li Q, Liu X, Wang Y, Liu J. FGG promotes migration and invasion in hepatocellular carcinoma cells through activating epithelial to mesenchymal transition. *Cancer Manag Res* 2019; **11**: 1653-1665 [PMID: 30863175 DOI: 10.2147/CMAR.S188248]

48 **Tang LQ**, Chen QY, Guo SS, Chen WH, Li CF, Zhang L, Lai XP, He Y, Xu YX, Hu DP, Wen SH, Peng YT, Liu H, Liu LT, Yan SM, Guo L, Zhao C, Cao KJ, Liu Q, Qian CN, Ma J, Guo X, Zeng MS, Mai HQ. The impact of plasma Epstein-Barr virus DNA and fibrinogen on nasopharyngeal carcinoma prognosis: an observational study. *Br J Cancer* 2014; **111**: 1102-1111 [PMID: 25051405 DOI: 10.1038/bjc.2014.393]

49 **Sheng L**, Luo M, Sun X, Lin N, Mao W, Su D. Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer. *Int J Cancer* 2013; **133**: 2720-2725 [PMID: 23716344 DOI: 10.1002/ijc.28284]

50 **Song H**, Kuang G, Zhang Z, Ma B, Jin J, Zhang Q. The Prognostic Value of Pretreatment Plasma Fibrinogen in Urological Cancers: A Systematic Review and Meta-analysis. *J Cancer* 2019; **10**: 479-487 [PMID: 30719143 DOI: 10.7150/jca.26989]

51 **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* 2000; **96**: 3302-3309 [PMID: 11071621]

52 **Guo Q**, Zhang B, Dong X, Xie Q, Guo E, Huang H, Wu Y. Elevated levels of plasma fibrinogen in patients with pancreatic cancer: possible role of a distant metastasis predictor. *Pancreas* 2009; **38**: e75-e79 [PMID: 19276866 DOI: 10.1097/MPA.0b013e3181987d86]

53 **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* 2015; **44**: 977-982 [PMID: 25931258 DOI: 10.1097/MPA.0000000000000353]

54 **Kakkar AK**, Levine MN, Kadziola Z, Lemoine NR, Low V, Patel HK, Rustin G, Thomas M, Quigley M, Williamson RC. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). *J Clin Oncol* 2004; **22**: 1944-1948 [PMID: 15143088 DOI: 10.1200/JCO.2004.10.002]

55 **Klerk CP**, Smorenburg SM, Otten HM, Lensing AW, Prins MH, Piovella F, Prandoni P, Bos MM, Richel DJ, van Tienhoven G, Büller HR. The effect of low molecular weight heparin on survival in patients with advanced malignancy. *J Clin Oncol* 2005; **23**: 2130-2135 [PMID: 15699479 DOI: 10.1200/JCO.2005.03.134]

56 **Lee AY**, Rickles FR, Julian JA, Gent M, Baker RI, Bowden C, Kakkar AK, Prins M, Levine MN. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of

patients with cancer and venous thromboembolism. *J Clin Oncol* 2005; **23**: 2123-2129 [PMID: 15699480 DOI: 10.1200/JCO.2005.03.133]

57 **Pengo V**, Noventa F, Denas G, Pengo MF, Gallo U, Grion AM, Iliceto S, Prandoni P. Long-term use of vitamin K antagonists and incidence of cancer: a population-based study. *Blood* 2011; **117**: 1707-1709 [PMID: 21127176 DOI: 10.1182/blood-2010-08-304758]

58 **Piccirillo JF**, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* 2004; **291**: 2441-2447 [PMID: 15161894 DOI: 10.1001/jama.291.20.2441]

59 **White RH**, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost* 2003; **90**: 446-455 [PMID: 12958614 DOI: 10.1160/TH03-03-0152]

60 **Khorana AA**, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. *Cancer* 2005; **104**: 2822-2829 [PMID: 16284987 DOI: 10.1002/cncr.21496]

61 **Campello E**, Ilich A, Simioni P, Key NS. The relationship between pancreatic cancer and hypercoagulability: a comprehensive review on epidemiological and biological issues. *Br J Cancer* 2019; **121**: 359-371 [PMID: 31327867 DOI: 10.1038/s41416-019-0510-x]

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