Retrospective Study

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

Li-Peng Zhang, Hu Ren, Yong-Xing Du, Xiao-Hao Zheng, Zong-Ming Zhang, Cheng-Feng Wang

ORCID number: Li-Peng Zhang 0000-0001-5204-6383; Hu Ren 0000-0001-7274-287X; Yong-Xing Du 0000-0003-3334-6561; Xiao-Hao Zheng 0000-0002-0282-1684; Zong-Ming Zhang 0000-0002-0797-7100; Cheng-Feng Wang 0000-0002-5589-7391.

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
Pancreatic cancer (PC) is a digestive system tumor with a poor prognosis and almost equal morbidity and mortality rates. It is the fourth leading cause of cancer-related death worldwide. The 5-year survival rate of PC patients in the United States is only 10%. 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. Radical resection has been accepted as an effective therapeutic choice that can significantly prolong the survival of patients with PC; it helps to reduce the perioperative mortality and complications of patients who undergo pancreatic surgery. However, there is no
significant improvement in the overall survival (OS) of patients with PC\cite{24}. The poor prognosis of PC patients is reported to be associated with asymptomatic onset\cite{25,26}, and a high risk of distant metastasis in the early stage\cite{27}. 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\cite{28}.

Patients with malignant tumors are generally in a hypercoagulable state, which leads to obvious thrombosis in the clinic\cite{19,20}. Cancer-associated venous thromboembolism (VTE) has become the second leading cause of death after the tumor itself\cite{21,22}, and the incidence of VTE is as high as 36% in PC patients\cite{23}. The occurrence and development of tumors can be promoted via the function of the coagulation/fibrinolysis system in a variety of ways\cite{24}.

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\cite{25}. Inflammation has been documented as one of the most important characteristics of cancer\cite{26}. 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\cite{27}.

The significance of tumor-related degradation products of the coagulation/fibrinolysis system has always been a hot research topic when evaluating patient prognosis\cite{28}. Elevated fibrinogen\cite{29} or D-dimer\cite{30} 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\cite{31}. 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\cite{32}); 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).
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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 \( \chi^2 \) 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)                                |                   |           |           |           |                       | 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 (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) | 0 (0) | 12 (13.0) | 2 (6.9) |
| T2       | 159 (56.4) | 0 (0) | 91 (98.9) | 0 (0) | 47 (51.1) | 21 (72.4) |
| T3       | 89 (31.6) | 0 (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) | 0 (0) |
| Present  | 121 (42.9) | 0 (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) | 0 (0) |
| N1       | 92 (32.6) | 0 (0) | 0 (0) | 92 (100.0) | 0 (0) | |
| N2       | 29 (10.3) | 0 (0) | 0 (0) | 0 (0) | 29 (100.0) | |
| Preoperative CA19-9 level (U/mL) | | | | | | 0.158 |
| > 336.4  | 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) |
| ≤ 336.4  | 77 (27.3) | 2 (10.0) | 21 (22.8) | 13 (26.5) | 31 (33.7) | 10 (34.5) |
| Preoperative fibrinogen concentration (g/L) | | | | | | 0.099 |
| > 3.31   | 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 (1.49-9.54) |
| ≤ 3.31   | 141 (50.0) | 8 (40.0) | 44 (47.8) | 30 (61.2) | 40 (43.5) | 19 (65.5) |
| Preoperative D-Dimer concentration (g/L) | | | | | | 0.099 |
| > 0.53   | 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) |
| ≤ 0.53   | 117 (41.5) | 8 (40.0) | 37 (40.2) | 23 (46.9) | 34 (37.0) | 15 (51.7) |
| 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.

Preoperative 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)                               | 72 (25.5)                            | 74 (26.2) | 0.812   |
| > 60                                   | 69 (24.5)                            | 67 (23.8) |         |
| ≤ 60                                   |                                     |         |         |
| Sex                                    | 71 (25.2)                            | 80 (28.4) | 0.283   |
| Female                                 | 70 (24.8)                            | 61 (21.6) |         |
| Blood type                             | 39 (13.8)                            | 48 (17.0) | 0.565   |
| A                                      | 51 (18.1)                            | 42 (14.9) |         |
| B                                      | 10 (3.5)                             | 12 (4.3)  |         |
| AB                                     | 41 (14.5)                            | 39 (13.8) |         |
| O                                      |                                     |         |         |
| Diabetes                               | 97 (34.4)                            | 104 (36.9)| 0.357   |
| Absent                                 | 44 (15.6)                            | 37 (13.1) |         |
| Smoking status                         | 107 (37.9)                           | 108 (38.3)| 0.889   |
| Absent                                 | 34 (12.1)                            | 33 (11.7) |         |
| Present                                | 121 (42.9)                           | 114 (40.4)|         |
| Alcohol consumption                    | 20 (7.1)                             | 27 (9.6)  | 0.263   |
| Absent                                 | 4 (1.4)                              | 7 (2.5)   |         |
| Present                                |                                     |         |         |
| Family history of cancer               | 137 (48.6)                           | 134 (47.5)| 0.356   |
| Absent                                 | 26 (9.0)                             | 27 (9.6)  |         |
| Present                                |                                     |         |         |
| 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 pancreaticectomy 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 < 0.001).
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)                               |                                    |         |
| > 60                                   | 65 (23.0)                          | 81 (28.7) | 0.284 |
| ≤ 60                                   | 52 (18.4)                          | 84 (29.8) |         |
| Sex                                    |                                    |         |
| Male                                   | 56 (20.6)                          | 93 (33.0) | 0.260 |
| Female                                 | 59 (20.9)                          | 72 (25.5) |         |
| Blood type                             |                                    |         |
| A                                      | 31 (11.0)                          | 56 (19.9) | 0.558 |
| B                                      | 40 (14.2)                          | 53 (18.8) |         |
| AB                                     | 9 (3.2)                            | 13 (4.6)  |         |
| O                                      | 37 (13.1)                          | 43 (15.2) |         |
| Diabetes                               |                                    |         |
| Absent                                 | 84 (29.8)                          | 117 (41.5) | 0.871 |
| Present                                | 33 (11.7)                          | 48 (17.0) |         |
| Smoking status                         |                                    |         |
| Absent                                 | 87 (30.9)                          | 128 (45.4) | 0.532 |
| Present                                | 30 (10.6)                          | 37 (13.1) |         |
| Alcohol consumption                    |                                    |         |
| Absent                                 | 101 (35.8)                         | 134 (47.5) | 0.256 |
| Present                                | 16 (5.7)                           | 31 (11.0) |         |
| Family history of cancer               |                                    |         |
| Absent                                 | 112 (39.7)                         | 159 (56.4) | 0.785 |
| Present                                | 5 (1.8)                            | 6 (2.1)  |         |
| Clinical symptoms                      |                                    |         |
| Absent                                 | 23 (8.2)                           | 34 (12.1) | 0.845 |
| Present                                | 94 (33.3)                          | 131 (46.5) |         |
| Open surgery approach                  |                                    |         |
| Pancreatoduodenectomy                  | 49 (17.4)                          | 81 (28.7) | 0.231 |
| Distal pancreatectomy with splenectomy | 68 (24.1)                          | 84 (29.8) |         |
| Tumor location                         |                                    |         |
| Head and neck                          | 49 (17.3)                          | 81 (28.7) | 0.231 |
| Body and tail                          | 68 (24.1)                          | 84 (29.8) |         |
| Degree of differentiation              |                                    |         |
| Well                                   | 18 (6.4)                           | 16 (5.7)  | 0.288 |
| Moderately                             | 85 (30.1)                          | 132 (46.8) |         |
| Poorly                                 | 14 (5.0)                           | 17 (6.0)  |         |
| Lymphovascular invasion                |                                    |         |
| Absent                                 | 83 (29.4)                          | 120 (42.6) | 0.742 |
| Present                                | 34 (12.1)                          | 45 (16.0) |         |
Perineural invasion & 0.001
|                | Present | Absent |
|----------------|---------|--------|
| Absent         | 76 (27.0) | 41 (14.5) |
| Present        | 136 (48.2) | 29 (10.3) |

Capsular invasion & 0.831
|                | Present | Absent |
|----------------|---------|--------|
| Absent         | 21 (7.4) | 28 (9.9) |
| Present        | 137 (48.6) | 76 (27.0) |

Maximal tumor diameter (cm) & 0.027
|                | ≥ 4 | ≤ 4 |
|----------------|----|----|
| Present        | 45 (16.0) | 72 (25.5) |
| Absent         | 43 (15.2) | 122 (43.3) |

T stage & 0.097
|                | T1 | T2 | T3 |
|----------------|----|----|----|
| Present        | 14 (5.0) | 58 (20.6) | 45 (16.0) |
| Absent         | 20 (7.1) | 101 (35.8) | 44 (15.6) |

Lymph node metastasis & 0.769
|                | Present | Absent |
|----------------|---------|--------|
| Absent         | 68 (24.1) | 93 (33.0) |
| Present        | 72 (25.5) | 49 (17.4) |

N stage & 0.356
|                | N0 | N1 | N2 |
|----------------|----|----|----|
| Present        | 68 (24.1) | 34 (12.1) | 15 (5.3) |
| Absent         | 93 (33.0) | 58 (20.6) | 14 (5.0) |

TNM stage & 0.608
|                | IA | IB | IIA | IIB | III |
|----------------|----|----|-----|-----|-----|
| Present        | 8 (2.8) | 37 (13.1) | 23 (8.2) | 34 (12.1) | 15 (5.3) |
| Absent         | 12 (4.3) | 55 (19.5) | 26 (9.2) | 58 (20.6) | 14 (5.0) |

Preoperative CA19-9 level (U/mL) & 0.056
|                | > 336.4 | ≤ 336.4 |
|----------------|---------|---------|
| Present        | 39 (13.8) | 78 (27.7) |
| Absent         | 38 (13.5) | 127 (45.0) |

Preoperative fibrinogen concentration (g/L) & 0.040
|                | > 3.31 | ≤ 3.31 |
|----------------|--------|--------|
| Present        | 67 (23.8) | 50 (17.7) |
| Absent         | 74 (26.2) | 91 (32.3) |

Adjuvant therapy & 0.268
|                | Present | Absent |
|----------------|---------|--------|
| 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)                                    |                  |         |
| > 60                                        | 1.358 (1.036-1.780) | 0.027   |
| ≤ 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                                     |                  |         |
| Perineurial 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 concentration are independent prognostic factors in PDAC patients undergoing radical R0 resection. Combining these factors may provide additional information for patient risk stratification.
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                                       | 0.669 (0.502-0.893) | 7.469  | 0.006   |
| Present                                      |                |        |         |
| Lymph node metastasis                        | 0.669 (0.502-0.893) | 7.469  | 0.006   |
| Absent                                       | 0.669 (0.502-0.893) | 7.469  | 0.006   |
| Present                                      | 0.669 (0.502-0.893) | 7.469  | 0.006   |
| Preoperative CA19-9 level (U/mL)             | 1.613 (1.387-2.191) | 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                                      | 1.620 (1.233-2.128) | 11.983 | 0.001   |

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.
| 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 (16.1)|
| Female                                  | 91 (32.3)                    | 40 (14.2)|
| Blood type                              |                              | 0.480   |
| A                                       | 54 (19.1)                    | 33 (11.7)|
| B                                       | 65 (23.0)                    | 26 (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   |
| Pancreateicoduodenectomy                | 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) |
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| Perineural invasion       |        |
|---------------------------|--------|
| Absent                    | 51 (18.1) | 19 (6.7) |
| Present                   | 140 (49.6) | 72 (25.5) |

| Capsular invasion         |        |
|---------------------------|--------|
| Absent                    | 29 (10.3) | 20 (7.1) |
| Present                   | 162 (57.4) | 71 (25.2) |

| Maximal tumor diameter (cm) |        |
|-----------------------------|--------|
| > 4                         | 68 (24.1) | 20 (7.1) |
| ≤ 4                         | 123 (43.6) | 71 (25.2) |

| T stage                    |        |
|---------------------------|--------|
| T1                         | 23 (8.2) | 11 (3.9) |
| T2                         | 99 (35.1) | 60 (21.3) |
| T3                         | 69 (24.5) | 20 (7.1) |

| Lymph node metastasis      |        |
|---------------------------|--------|
| Absent                    | 111 (39.4) | 50 (17.7) |
| Present                   | 80 (28.4) | 41 (14.5) |

| N stage                    |        |
|---------------------------|--------|
| N0                         | 111 (39.4) | 50 (17.7) |
| N1                         | 55 (19.5) | 37 (13.1) |
| N2                         | 25 (8.9) | 4 (1.4) |

| TNM stage                  |        |
|---------------------------|--------|
| 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) |        |
|----------------------------------|--------|
| > 336.4                          | 58 (20.6) | 19 (6.7) |
| ≤ 336.4                          | 133 (47.2) | 72 (25.5) |

| Adjuvant therapy                |        |
|---------------------------------|--------|
| 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                        |                  |       |         |          |
| Low-low group                         |                  |       |         |          |
| 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[28]. 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
in the systemic inflammatory response as an acute inflammatory protein\textsuperscript{[18]}, and the latter is a key factor in the occurrence and development of many malignant tumors, including PC\textsuperscript{[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\textsuperscript{[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\textsuperscript{[40]}. Moreover, fibrinogen can bind directly to growth factors that function significantly in angiogenesis, tumor proliferation and metastasis\textsuperscript{[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\textsuperscript{[44,45]}. It is important to note that fibrinogen can further enhance the invasion and metastasis of tumor cells through EMT\textsuperscript{[46,47]}. Recent clinical studies have documented that the fibrinogen concentration is negatively correlated with the prognosis of solid malignancies\textsuperscript{[22]}, such as head and neck cancer\textsuperscript{[48]}, non-small cell lung cancer\textsuperscript{[49]}, gallbladder cancer\textsuperscript{[50]}, and urinary system tumors\textsuperscript{[51]}, and can predict distant metastasis\textsuperscript{[51]}. The preoperative fibrinogen concentration showed a positive correlation with the stage of PC\textsuperscript{[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, \( P < 0.001 \))\textsuperscript{[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\textsuperscript{[54-56]}, and vitamin K antagonists play a protective role in cancer patients\textsuperscript{[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\textsuperscript{[58]}, surgical approaches and the duration\textsuperscript{[59]}, and toxicity of chemotherapy\textsuperscript{[60]}. Hypercoagulability in PC patients is a consequence of the combined action of the coagulation-promoting factors of tumor cells themselves and their microenviroment.
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.

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