

Elevated pretreatment plasma D-dimer levels and platelet counts predict poor prognosis in pancreatic adenocarcinoma

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Abstract: This retrospective study was conducted to evaluate the prognostic significance of the preoperative plasma D-dimer levels and platelet counts in patients with pancreatic adenocarcinoma. A total of 168 consecutive locally advanced pancreatic adenocarcinoma patients who underwent intensity modulated radiation therapy with or without chemotherapy were enrolled in this study. Plasma D-dimer levels were measured by a latex-enhanced immunoturbidimetric assay. Of the 168 patients enrolled, 106 patients were males and 62 patients were females. There was significant difference between plasma D-dimer levels and clinical responses ($P=0.001$). The 1-year, 2-year, and 3-year cumulative overall survival rates were 50.6%, 15.0%, and 4.9%, respectively. Plasma D-dimer levels ($P<0.001$) and platelet counts ($P=0.010$) were significantly related with overall survival in univariate analysis. The Cox proportional hazards regression indicated that plasma D-dimer levels ($P=0.028$), platelet counts ($P=0.004$), and treatment response ($P<0.001$) were independent prognostic factors for overall survival. Elevated pretreatment plasma D-dimer levels and platelet counts predict poor prognosis in pancreatic adenocarcinoma.

Keywords: pancreatic adenocarcinoma, D-dimer, platelet counts, prognosis, radiotherapy

Introduction

Pancreatic adenocarcinoma is one of the most extremely malignant neoplasms among all types of cancer in both developing and developed countries.¹ The prognosis remains quite poor, with a great number of patients experiencing disease progression in a very short time. Radical surgery is thought to be the only therapy that can provide opportunity for cure and long-time survival.² However, only 10%–20% of the patients could be candidate for surgical pancreatectomy according to previous reports.^{3,4} For locally advanced pancreatic adenocarcinoma, combined or sequential chemotherapy and radiotherapy is the standard treatment.⁵ Several studies have attempted to discover molecular biomarkers to predict the prognosis of pancreatic adenocarcinoma.^{6,7} However, to date, most of these markers had not been proven to be sufficiently effective.⁸

The relationship between coagulation and cancer has been studied for more than a century. Recently, coagulation activation, in particular fibrin formation and dissolution, has been implicated in tumor invasion, metastases, and eventual worse outcome in pancreatic adenocarcinoma.^{9,10} Several studies reported that pretreatment plasma D-dimer levels or platelet counts were prognostic factors in pancreatic adenocarcinoma.^{10,11} However, majority of these reports focused on metastatic pancreatic adenocarcinoma and the sample was relatively small (less than 80 patients). Therefore, the aim of this study was to determine whether the plasma D-dimer levels and platelet counts before chemoradiotherapy are predictors of mortality in patients with locally advanced unresectable pancreatic adenocarcinoma.

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Patients and methods

This survival study was carried out in 168 locally advanced unresectable consecutive pancreatic adenocarcinoma patients who received gemcitabine-based chemoradiotherapy in Zhejiang cancer hospital. All patients were newly confirmed to have pancreatic adenocarcinoma and had not received treatment previously. Patients with other malignancies were excluded from this study. Each case was reassigned for tumor, regional lymph node metastases, and distant organ metastases (tumor node metastasis [TNM] stage) classification and clinical stage according to the American Joint Committee on Cancer (AJCC) staging system.¹² The following detail clinical information was retrospectively collected and analyzed for each case: sex, age at treatment, smoking status, tumor location, clinical TNM stage, treatment response, and overall survival (OS) after treatment. Our study was approved by the institutional review board and ethics committee of the hospital. All patients provided informed consent before chemoradiotherapy. OS was calculated as the time from radiotherapy to death or censoring.

Each patient provided two 5 mL blood samples pre-treatment. Plasma D-dimer levels were measured by a latex-enhanced immunoturbidimetric assay using a Sysmex CA 7000 (Sysmex Corp, Kobe, Japan) analyzer in Zhejiang cancer hospital. Plasma D-dimer levels $\leq 0.5 \mu\text{g/mL}$ was used as cutoff for normal versus high D-dimer values, according to the manufacture's recommendation. A complete blood count was regularly taken, and high group was defined as platelet count greater than $300 \times 10^9/\text{L}$.

Treatment schedule

All patients were treated with intensity modulated radiation therapy (IMRT). Patients were immobilized in a supine position, arms overhead, with thermoplastic cast. Patients underwent CT-simulation on CT scanner (GE, Lightspeed, USA), using 5 mm slices with contrast enhancement. Radiation plans for IMRT were generated using Pinnacle Version 8.0. All patients underwent external beam radiation therapy with 6 MV X-rays. The area of solid macroscopic tumors in pancreas, the surrounding tissue infiltrated, and the regional lymph node metastases were defined as the gross tumor volume (GTV). The GTV plus a margin of at least 5 mm, including any areas of microscopic spread and the regional lymph nodes (peripancreatic, celiac, superior mesenteric, portal hepatic, retroperitoneal), was defined as the clinical target volume (CTV). The plan target volume (PTV) was defined as the CTV plus 0.5–1.0 cm to account for the daily setup variation and respiratory movement. A fractional daily dose of 1.8 Gy (Gray) (5 days per week, over 5 weeks) at

an isocenter was prescribed. The median delivered dose of IMRT was 50 Gy (range: 44.0–55.8 Gy). The dose to the adjacent normal structures was constrained as follows: The liver dose was limited to $V_5 < 75\%$, $V_{20} < 50\%$, $V_{30} < 30\%$, and a mean dose less than 28 Gy. The kidney dose was limited to $V_{12} < 50\%$ and $V_{22.5} < 30\%$. Spinal cord maximum dose was held to 45 Gy. The CTV encompassed at least 95% isodose line. The dose volume histogram (DVH) was obtained for CTV, PTV, spinal cord, liver, and kidney. The small bowel contour was confined to the small bowel loops within 3 cm of the PTV and was limited to maximal dose < 54 Gy.

Concurrent chemoradiotherapy, with or without adjuvant chemotherapy, was used in 103 patients. The chemotherapy regimens consisted of S1 at 50 mg/m² twice daily from days 1 to 14 or gemcitabine at 1,000 mg/m² on day 1 and day 8 of a 21 days cycle. The CR (complete response), PR (partial response), SD (stable disease), and PD (progressive disease) were assessed at an interval of at least 4 weeks to confirm the objective response. All patients received standardized follow-up, occurring at 3 months interval for 2 years, 6 months interval the 3rd year, and yearly thereafter. Evaluations comprised a physical examination, pancreatic CT, complete blood count, liver and kidney function tests, abdominal ultrasound, chest radiography, and pelvic CT.

Statistical analysis

Data was presented as median \pm standard error. The chi-square test was performed to evaluate the association between the clinicopathological variables and plasma D-dimer levels or platelet counts. OS time was defined as the time interval from the initial event (radiotherapy) to the death or censoring. Survival curves were estimated by the univariate Kaplan–Meier method. The log-rank test was applied to check the significant difference in the curves among groups. Furthermore, we used the Cox proportional hazards model with the backward selection method for multivariate analysis. All statistical calculations were performed with SPSS 13.0 software for Windows (Chicago, IL, USA). Two-sided *t*-test *P*-values of < 0.05 were considered to be statistically significant.

Results

Characteristics of patients

The characteristics of these patients are summarized in Table 1. Of the 168 patients enrolled, 106 patients were males and 62 patients were females. The study population had a median age of 61 years (range: 34–83 years). On the basis of image parameters, tumor was found with regional lymph node metastases in 89 (53.0%) patients. The numbers of T₁, T₂, T₃, and T₄

Table 1 Relationship between clinicopathological parameters, plasma D-dimer levels (>0.5 µg/mL vs ≤0.5 µg/mL), and platelet counts (>300×10⁹/L vs ≤300×10⁹/L) in 168 patients with pancreatic adenocarcinoma

Variable	Total, n	D-dimer			Platelet counts		
		≤0.5 µg/mL	>0.5 µg/mL	P-value	≤300×10 ⁹ /L	>300×10 ⁹ /L	P-value
Sex				0.435			0.596
Male	106	25 (23.6)	81 (76.4)		91 (85.8)	15 (14.2)	
Female	62	18 (29.0)	44 (71.0)		55 (88.7)	7 (11.3)	
Age (years)				0.911			0.885
≤65	120	31 (25.8)	89 (74.2)		104 (86.7)	16 (13.3)	
>65	48	12 (25.0)	36 (75.0)		42 (87.5)	6 (12.5)	
Tumor location				0.432			0.764
Head	79	18 (22.8)	61 (77.2)		68 (86.1)	11 (13.9)	
Body and tail	89	25 (28.1)	64 (71.9)		78 (87.6)	11 (12.4)	
Chemotherapy				0.621			0.485
Yes	103	25 (24.3)	78 (75.7)		91 (88.3)	12 (11.7)	
No	65	18 (27.7)	47 (72.3)		55 (84.6)	10 (15.4)	
Tumor size				0.381			0.499
≤4 cm	88	25 (28.4)	63 (71.6)		75 (85.2)	13 (14.8)	
>4 cm	80	18 (22.5)	62 (77.5)		71 (88.8)	9 (11.3)	
T stage				0.322			0.328
T1–T2	45	14 (31.1)	31 (68.9)		41 (91.1)	4 (8.9)	
T3–T4	123	29 (23.6)	94 (76.4)		105 (85.4)	18 (14.6)	
N stage				0.874			0.782
N0	79	69 (87.3)	10 (12.7)		21 (26.6)	58 (73.4)	
N1	89	77 (86.5)	12 (13.5)		22 (24.7)	67 (75.3)	
Serum CA199 ^a				0.894			0.584
≤37 U/mL	82	19 (23.2)	63 (76.8)		71 (86.6)	11 (13.4)	
>37 U/mL	58	14 (24.1)	44 (75.9)		52 (89.7)	6 (10.3)	
Serum CA125 ^b				0.771			0.690
≤35 U/mL	27	7 (25.9)	20 (74.1)		23 (85.2)	4 (14.8)	
>35 U/mL	133	31 (23.3)	102 (76.7)		117 (88.0)	16 (12.0)	
Serum CEA ^c				0.846			0.969
≤5 ng/mL	102	26 (25.5)	76 (74.5)		89 (87.3)	13 (12.7)	
>5 ng/mL	54	13 (24.1)	41 (75.9)		47 (87.0)	7 (13.0)	
Response				0.001			0.315
CR+PR	62	25 (40.3)	37 (59.7)		56 (90.3)	6 (9.7)	
SD+PD	106	18 (17.0)	88 (83.0)		90 (84.9)	16 (15.1)	

Notes: Bold value is statistically significant ($P<0.05$). ^a28 patients' data were missing; ^b8 patients' data were missing; ^c12 patients' data were missing.

Abbreviations: CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

tumor patients were 17 (10.1%), 28 (16.7%), 77 (45.8%), and 46 (27.4%), respectively. The size of tumor was between 2.2 and 10 cm in most pancreatic adenocarcinomas.

Plasma D-dimer levels, platelet counts, and characteristics of patients

The median of plasma D-dimer levels and platelet counts in total patients was 1.03 µg/mL (range: 0.11–6.45 µg/mL) and 169×10⁹/L (range: 54–696×10⁹/L). Plasma D-dimer levels were above 0.5 µg/mL in 125 patients (74.4%). The incidence of high platelet counts was 13.1% (22/168). No significant correlation was observed between clinical parameters (like sex, age, tumor location, tumor size, T stage, and N stage) and plasma D-dimer levels or platelet counts

($P>0.05$, Table 1). There were 14 patients who had a CR, and 48, 99, and 7 patients had PR, SD, and PD, respectively. There was significant difference between plasma D-dimer levels and clinical responses ($P<0.001$). There was a higher ratio of SD and PD for the patients with high plasma D-dimer levels (83.0%) than those with normal plasma D-dimer levels (17.0%). However, no significant difference was observed between platelet counts and treatment response ($P>0.05$).

Prognostic relevance of clinicopathological parameters, plasma D-dimer, and platelet counts

The follow-up was conducted from 3 to 48 months with a median period of 14 months. During the follow-ups,

148 patients (88.1%) died of disease progression. The 1-year, 2-year, and 3-year cumulative OS rates were 50.6%, 15.0%, and 4.9%, respectively. We evaluated the prognostic values of the pretreatment plasma D-dimer, platelet counts, and other clinicopathological parameters, as shown in Table 2. Compared with high levels of plasma D-dimer, normal levels owned a better 2-year OS rate (18.1% vs 9.9%, $P < 0.001$, Figure 1). The median OS time was shorter in patients with platelet counts $>300 \times 10^9/L$ than in those with platelet

Table 2 Prognostic relevance of clinicopathological parameters, plasma D-dimer levels, and platelet counts in the univariate analysis

Variables	n	MST (months)	2-year survival (%)	P-value
Sex				0.824
Male	106	12	13.2	
Female	62	12	16.3	
Age (years)				0.997
≤ 65	120	12	14.0	
> 65	48	11	17.5	
Tumor location				0.146
Head	79	11	13.0	
Body and tail	89	13	15.3	
Chemotherapy				0.089
Yes	103	12	17.9	
No	65	10	7.3	
Tumor size				0.736
≤ 4 cm	88	12	12.0	
> 4 cm	80	11	18.2	
T stage				0.738
T1–T2	45	13	16.5	
T3–T4	123	11	14.5	
N stage				0.035
N0	79	14	16.5	
N1	89	11	13.3	
Serum CA199 ^a				0.023
≤ 37 U/mL	82	13	17.1	
> 37 U/mL	58	10	5.9	
Serum CA125 ^b				0.612
≤ 35 U/mL	27	12	14.4	
> 35 U/mL	133	12	16.2	
Serum CEA ^c				0.057
≤ 5 ng/mL	102	13	18.0	
> 5 ng/mL	54	11	8.8	
Response				< 0.001
CR+PR	62	16	33.3	
SD+PD	106	9	2.4	
Plasma D-dimer				< 0.001
≤ 0.5 $\mu\text{g/mL}$	43	16	18.1	
> 0.5 $\mu\text{g/mL}$	125	10	9.9	
Platelet counts				0.010
$\leq 300 \times 10^9/L$	146	12	13.2	
$> 300 \times 10^9/L$	22	9	4.5	

Notes: Bold values are statistically significant ($P < 0.05$). ^a28 patients' data were missing; ^b8 patients' data were missing; ^c12 patients' data were missing.

Abbreviations: MST, median survival time; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

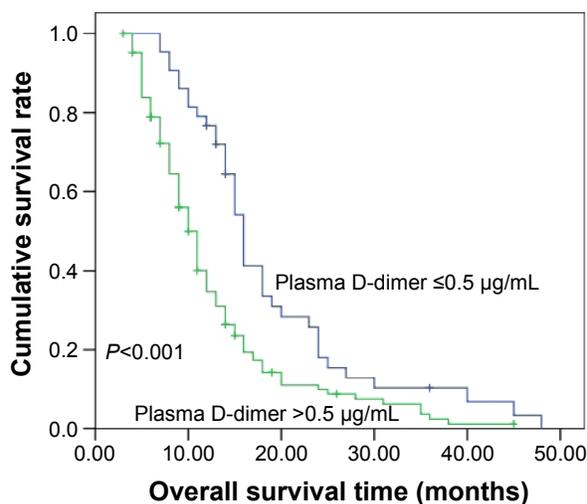


Figure 1 Cumulative survival curves for overall survival time according to pretreatment plasma D-dimer levels.

counts $\leq 300 \times 10^9/L$ (9 months vs 12 months, $P = 0.010$, Figure 2). Additionally, lymph node metastases ($P = 0.035$), plasma CA 199 levels ($P = 0.023$), and treatment response ($P < 0.001$) were significantly related with OS in univariate analysis.

We performed multivariate analysis on the factors that were statistically significant in the univariate analysis. The results are shown in Table 3. The Cox proportional hazards regression indicated that plasma D-dimer levels ($P = 0.028$), platelet counts ($P = 0.004$), and treatment response ($P < 0.001$) were independent prognostic factors for OS.

Discussion

Recently, more attention has been given to the association between the progression of malignancies and coagulation. Hypercoagulability is a sign of a more aggressive disease. Elevated plasma D-dimer levels and platelet counts are

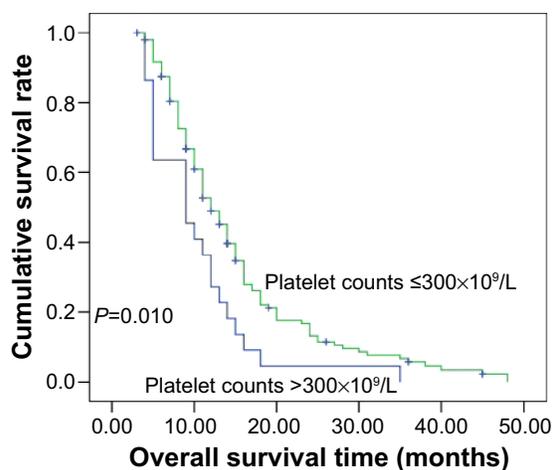


Figure 2 Cumulative survival curves for overall survival time according to pretreatment platelet counts.

Table 3 Prognostic relevance of N stage, serum CA199 levels, plasma D-dimer levels, platelet counts, and treatment response in the multivariate analysis

Variables	HR	95% CI	P-value
N stage (N0 vs N1)	0.77	0.53–1.11	0.167
Serum CA199 levels (>37 U/mL vs ≤37 U/mL)	1.34	0.91–1.97	0.137
Plasma D-dimer levels (>0.5 µg/mL vs ≤0.5 µg/mL)	1.65	1.06–2.59	0.028
Platelet counts (>300×10 ⁹ /L vs ≤300×10 ⁹ /L)	2.23	1.30–3.83	0.004
Response (SD+PD vs CR+PR)	3.10	1.98–4.87	<0.001

Note: Bold values are statistically significant ($P < 0.05$).

Abbreviations: HR, hazard ratio; CI, confidence interval; CA199, carbohydrate antigen 199; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

correlated with worse outcome in patients with epithelial ovarian cancer,¹³ lung cancer,¹⁴ and colorectal cancer.¹⁵ In this study, we find that elevated pretreatment plasma D-dimer levels and platelet counts were associated with poorer prognosis in pancreatic adenocarcinoma patients receiving IMRT. Patients with elevated plasma D-dimer levels had 1.65 times the risk of death compared with those with normal plasma D-dimer levels. Patients with platelet counts $>300 \times 10^9/L$ had 2.23 times the risk of death compared with those with platelet counts $\leq 300 \times 10^9/L$.

D-dimer is a stable fibrin degradation product. Plasma D-dimer is a marker of hypercoagulation, usually used for the assessment of suspect venous thromboembolism.¹⁶ Increased plasma D-dimer levels are also observed in patients with myocardial infarction, infectious disease, trauma, and pregnancy.¹⁷ There are several reports regarding the role of plasma D-dimer in patients with pancreatic adenocarcinoma. Durczynski et al¹⁸ analyzed 64 potentially resectable pancreatic tumor without detectable venous thrombosis. Only 45.3% of the patients enrolled were found to be resectable. High plasma D-dimer levels can predict the unresectability of pancreatic cancer. There have also been reports regarding the prognostic significance of the D-dimer level in patients with pancreatic cancer. In a retrospective study,¹⁹ 73 pancreatic cancer were followed over 2 years. Elevated plasma D-dimer levels are associated with poor prognosis according to multivariate survival analysis. However, this study did not determine whether the increased mortality among pancreatic cancer patients with elevated plasma D-dimer levels is independent of venous thromboembolism. Furthermore, the sample in this study is small. The author did not present the detailed information about the tumor stage and treatment regimen. Platelets serve various roles in physiological pathways, including

coagulation and inflammation. Increased platelet counts at the time of diagnosis are associated with significantly short survival time among patients with solid tumors.²⁰ Brown et al²¹ undertook a chart review of patients undergoing resection for pancreatic adenocarcinoma. They analyzed 109 patients with resected pancreatic adenocarcinoma and found that platelet counts are independent prognostic biomarkers for OS in operable pancreatic cancer. Similarly, Dominguez et al²² reported the prognostic significance of the platelet count based on an analysis of operable 205 patients with pancreatic ductal adenocarcinoma. Although these results somewhat overlapped with present study, we have additionally adjusted for some strong prognostic factors, such as CA199 and treatment response. Therefore, the strength of the current study was direct comparison of plasma D-dimer levels and platelet counts in pancreatic adenocarcinoma under the same treatment. Also, it seems more homogeneous because no postoperative venous thromboembolism events were found during the follow-up.

However, the exact mechanism underlying D-dimer mediated pancreatic adenocarcinoma progression remains unclear. Tumor cells could convert fibrinogen to fibrin. D-dimer, which is a stable fibrinogen degradation product, was shown to be associated with tumor progression and an elevated plasma D-dimer levels may reflect ongoing fibrinogen metabolism within actively remodeling tumor stroma.²³ Second, increased expression of tissue factor, which is also expressed by tumor cells, will activate coagulation cascades and ultimately lead to fibrin deposition, tumor growth, and tumor cell metastases.²⁴ Furthermore, plasma D-dimer levels may reflect the presence of micrometastases or circular tumor cells, which may be responsible for tumor recurrence.²⁵ The formation of a clot around the tumor cells in the circulation also prevents the tumor cells from being killed by natural killer cells.²⁶ The exact reason for the association between elevated platelet counts and worse outcome of pancreatic adenocarcinoma still remains unknown. Increased platelet counts may promote tumor cell growth and angiogenesis. Platelets release various cytokines, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), during blood clotting. The VEGF and PDGF family of proteins play significant roles in regulating angiogenesis. The invasiveness of the cancer cells may be enhanced by the plasma components in stored platelets.²⁰

Our study has several limitations. Our study may be limited by the relatively small sample analyzed and retrospective design. Second, plasma D-dimer levels and platelet counts were checked only once in each patient and were not examined during the follow-up. Furthermore, the follow-up time was relatively

short and information on posttreatment recurrence was insufficient, which we are planning to analyze in the future.

Our results suggest that pretreatment plasma D-dimer levels and platelet counts could be served as new independent prognostic biomarkers for OS in pancreatic adenocarcinoma. Plasma D-dimer levels and platelet counts should be assessed in the workup of patients with pancreatic adenocarcinoma in future trials to confirm their prognostic significance.

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Disclosure

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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