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Pre-Chemotherapy D-Dimer Levels as Predictors of Survival Outcomes in Advanced Gastric Cancer

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Background: Gastric cancer is a common malignancy of the digestive system. There are presently no efficacious indicators to evaluate its curative effect and prognosis. Increased plasma D-dimer was reported to have a very strong association with neoplasm in advanced stages and poor overall survival (OS) for some malignant tumors in morbidity.

Material/Methods: Using propensity score analysis, we examined the potential effect of pre-chemotherapy plasma D-dimer level (PDL) on OS and progression-free survival (PFS) in patients with advanced gastric cancer (AGC). We divided 134 patients with AGC into 2 groups: low pretreatment D-dimer (LPD) and high pretreatment D-dimer (HPD). Using propensity score analysis, one-to-one matches were performed for both groups to correct bias caused by different covariate distributions.

Results: Before matching, patients with HPD had obviously lower median OS and PFS versus patients with LPD (months: 6.0 vs 8.7, *P*=0.015; 12.2 vs 15.1, *P*=0.037). Multivariate analysis indicated that PDL did not independently predict OS (hazard ratio [HR] 1.362, 95% confidence interval (CI) 0.851-2.181, *P*=0.198). In accordance with the first response evaluation, patients with PD had an increased mean D-dimer by 1.72 ug/mL compared with patients with PR and SD (*P*=0.006). There was a 15.1-month median OS for patients with LPD compared to 12.2 months for those with HPD (*P*=0.032). Multivariate analysis discovered that OS was independently predicted by PDL (HR of 1.711, 95% CI of 1.019 to 2.875, *P*=0.042), and the first response evaluation's mean D-dimer was raised by 1.91 ug/mL in patients with PD (*P*=0.039).

Conclusions: Gastric cancer patients with high D-dimer level had worse outcomes.

Keywords: Prognosis • Survival Analysis • Cancer Survivors

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Introduction

Gastric cancer causes around 770 000 deaths worldwide each year, and is the fourth-leading cause of cancer-associated mortality [1]. The 5-year overall survival (OS) rate of patients with advanced gastric cancer (AGC) has improved from 23% to 45%, but the prognosis remains unsatisfactory [2-4].

For AGC, systemic chemotherapy is a standard therapy, but biomarkers for predicting gastric cancer outcome are scarce. The main treatment option for AGC that cannot be resected is systemic chemotherapy. During the last decade, use of antibodies against epidermal growth factor receptors and antibodies against vascular endothelial growth factor have improved OS rates. It is significantly simpler and less costly to measure prognostic serum biomarkers for AGC than to use tissue-based biomarkers. In the past few decades, biomarkers have been explored to predict the occurrence and OS of AGC.

Patients with malignant tumors have hypercoagulability as a physiological characteristic. It is essential for tumor angiogenesis that fibrin undergoes extra-cellular remodeling. D-dimer is the result of tissue plasminogen activator degrading cross-linked fibrin factor XIIIa through generating plasmin from plasminogen. By producing a monoclonal antibody that recognizes neither fibrinogen degradation nor non-cross-linked fibrin, it has been easier to investigate human D-dimer levels. Despite the absence of thrombosis, patients with advanced-stage tumors often have a systemic hypercoagulable state [5,6]. Patients (above 90%) with metastatic lesions had abnormal clotting or fibrinolysis, containing antithrombin-III (AT-III) complexes fibrinopeptides A (FPA) and D-dimer [7]. Venous thromboembolism (VTE) is an often-overlooked cause of mortality and morbidity in cancer patients can it is easily prevented and treated [8]. Specifically, a high risk of VTE is strongly associated with gastric cancer [9]. Blood flow stasis, endothelial damage, and hypercoagulability are all associated with VTE in cancer patients [10].

In cancer patients, D-dimer is a biomarker that can be used to diagnose and treat thrombosis, but it is rarely used to identify tumors. The predictive and prognostic value of D-dimer in AGC needs to be validated. Research shows that thrombin activatable fibrinolysis inhibitor (TAFI) and thrombin-antithrombin (TAT) complex levels [11], along with the stage IV patients' D-dimer levels, were elevated in 52 gastric cancer patients. One study involving 1178 patients of lifetime beyond 2 years discovered that a subgroup of 50 gastric cancer patients had higher plasma D-dimers, which was linked to poorer OS and a notable risk factor for death [12]. Fibrinolytic activity induced by plasmin produced D-dimer as a cross-linked fibrin degradation product. Researchers have found that D-dimers advance cell proliferation and provoke angiogenesis in addition to affecting cellular signaling systems [13], as well as induce tumor growth and spread by motivating cancer cells to adhere to cells of endothelium, affecting platelets and the extra-cellular matrix (ECM) [14].

No long-term research has examined the linkage exists in plasma D-dimer levels and OS in AGC patients. This is the first study to analyze the effect of D-dimer on prognosis of patients with advanced gastric cancer by using propensity matching. We corrected the error due to different distributions of covariates by using Cox proportional hazard regression and propensity score matching. The goal was to estimate how PDL affects the prognosis of patients with AGC.

Material and Methods

Patient Selection

Patients newly diagnosed with histologically substantiated advanced gastric malignancy receiving chemotherapy at the Sixth Medical Center, Chinese PLA General Hospital between January 2019 and December 2023 were identified from a retrospective archival database of electronic records. They all had metastatic gastric cancer and had IV stage tumors. The inclusion criteria were: 1) gastric cancer patients aged ≥18 years and with pathologically and/or computed tomography (CT) proven AGC; 2) no prior palliative therapies (containing chemotherapy and radiotherapy); and 3) followed up at least once. The exclusion criteria were: 1) breastfeeding or pregnant women; 2) previous malignancy diagnosed, a concurrent malignancy was present, or secondary tumors; 3) medical histories associated with thromboembolism, familial coagulopathy, active infections, or disseminated intravascular coagulation; 4) anti-coagulant and anti-aggregate therapies; 5) missing data on PDL; 6) underwent adjuvant chemotherapy after surgical resection.

Follow-Up

The study enrolled 134 patients after excluding 16 patients, as shown in **Figure 1**. The control group consisted of 89 patients with advanced gastric malignancy and low plasma D-dimer level. The data from both groups are summarized in **Table 1**. The study was reviewed and approved by the Ethics Committee of the Sixth Medical Center, Chinese PLA General Hospital. There were 134 AGC patients at the Sixth Medical Center, Chinese PLA General Hospital between January 2019 and December 2023 who were eligible for this study. Follow-up data were obtained by review of hospital records, communication with patients' families, and reviews of the Sixth Medical Center, Chinese PLA General Hospital Registry. Patients were followed up until June 30, 2024. OS time is the interval between when gastric cancer was diagnosed and last follow-up or death.

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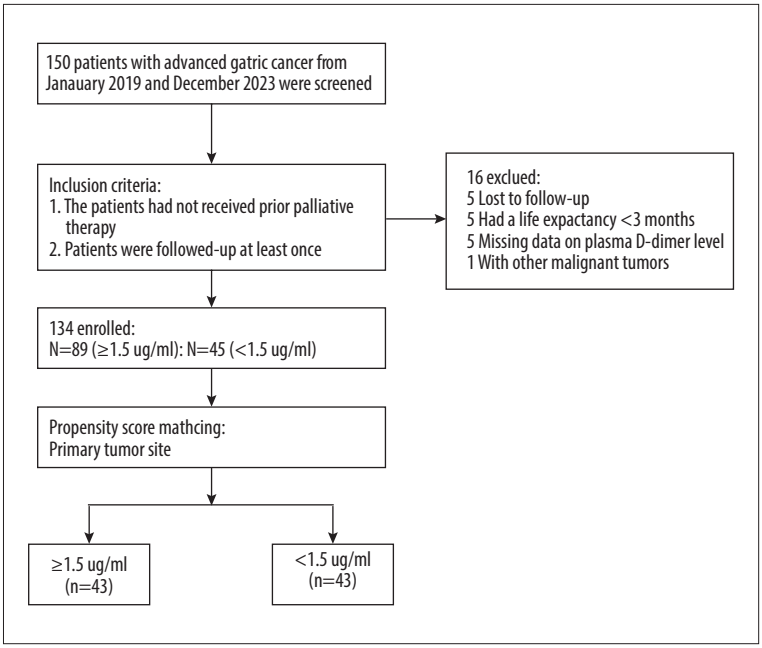

Figure1. Trial profile.

Enzyme-Linked Fluorescent Immunoassays for D-Dimer Levels

Among advanced gastric malignancy patients undergoing chemotherapy or radiotherapy, venous blood samples were collected and enzyme-linked fluorescent immunoassays and the mini-Vidas device (BioMerieux SA) were used to measure D-dimer levels. D-dimer levels over 1.5 ug/ml were considered HPD.

Statistical Analyses

Comparing categorical data was done applying chi-square tests or Fisher's exact tests. Contrasting continuous data were assesses using the *t* test or Mann-Whitney U test. The survival benefits of these 2 treatments were compared using Kaplan-Meier survival curves and log-rank test. Multivariate and univariate analyses were performed using Cox proportional hazard regression models. The Wilcoxon signed-rank test was used to compare the samples of the 2 pairs. Analysis of multivariate survival data was conducted after univariate survival variables with *P* values >0.05 were incorporated. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated for each predictor of survival. Since patients were not assigned to LPD or HPD at random, we reduced selection bias and balanced potential confounders. Applying propensity score matching (PSM), the following variables were included in the propensity model: sex, age, tumor location, tumor size, histology, pathological diagnosis, chemotherapy cycles, CEA, CA199, and CA724. $P<0.05$ (2-sided) was regarded as indicating a statistically significant difference. The propensity score indicates the conditional probability of a subject receiving a treatment given a vector of covariates, and is often used in non-randomized studies to adjust selection bias. A caliper of 0.02 was applied to the logit of the propensity score's standard deviation. Each of the statistical analyses above was carried using SPSS software, version 25.0 (IBM, Chicago, IL, USA).

Results

The Clinical and Pathological Features of the Entire Study Series Prior to Matching

The vast majority (145 [96.7%]) of the 150 patients were followed up at least once. There were 134 patients included in the analysis after 16 patients were excluded. The follow-up time was 12.0 months on average (range: 3-50) (**Figure 1**). The 134 included patients consisted of 99 males (73.9%) and 35 females (26.1%). The median age was 63 years, with a range of 29-79 years. There were 26 of the 150 recruited patients who were not tested for HER-2 status, and 15 (12.1%) of these 124 patients were HER-2 positive, and these 15 patients received trastuzumab for chemotherapy. A total of 134 patients received chemotherapy using 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX6) or capecitabine and oxaliplatin (XELOX) or paclitaxel and cisplatin (TP) or docetaxel, oxaliplatin and S-1(DOS). Prior to the first treatment evaluation, 2 cycles of chemotherapy had been finished. In conformity with the Response Evaluation Criteria in Solid Tumors, version 1.1, computed tomography (CT) or magnetic resonance imaging (MRI) was used to determine treatment response. The objective responses were classified as partial responses (PRs), stable diseases (SDs), and progressive diseases (PDs).

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Table 1. Baseline characteristics.

	Low pretreatment D-dimer (<1.5 ug/ml, n=89)	High pretreatment D-dimer (≥1.5 ug/ml, n=45)	P
Median age, y	63 (range: 32-78)	64 (range: 29-79)	0.276
Sex			
Male	70 (78.7%)	29 (64.4%)	0.077
Female	19 (21.3%)	16 (35.6%)	
Histology			
p/d or p-m/d	46 (95.8%)	22 (88.0%)	0.331
m/d or m-w/d	2 (4.2%)	3 (12.0%)	
Pathological diagnosis			
Adenocarcinoma	81 (91.0%)	41 (91.1%)	0.495
Signet-ring cell carcinoma	3 (3.4%)	3 (6.7%)	
Others	5 (5.6%)	1 (2.2%)	
Tumor location			
Upper one-third	44 (49.4%)	15 (33.3%)	0.025
Middle one-third	28 (31.5%)	12 (26.7%)	
Lower one-third	17 (19.1%)	16 (35.6%)	
Whole	0	2 (4.4%)	
Site of metastasis			
Liver only	18 (20.2%)	8 (17.8%)	0.162
LN only	20 (22.5%)	8 (17.8%)	
LN+liver	28 (31.5%)	15 (33.3%)	
Abdominal	20 (22.5%)	7 (15.6%)	
Bone	3 (3.4%)	7 (15.6%)	
Tumor size			
<50 cm	84 (94.4%)	43 (95.6%)	1.000
≥50 cm	5 (5.6%)	2 (4.4%)	
Elevated CEA# (n=76)	48 (63.2%)	28 (36.8%)	0.345
Elevated CA199## (n=58)	34 (58.6%)	24 (41.4%)	0.092
Elevated CA724* (n=53)	32 (60.4%)	21 (39.6%)	0.185
Median no. Of CTx cycles	8 (2-32)	8 (2-27)	0.653
Best response			
PR	29 (32.6%)	15 (33.3%)	0.515
SD	45 (50.6%)	19 (42.2%)	
PD	15 (16.9%)	11 (24.4%)	
Her-2 (n=124)			
Positive	7 (14.3%)	8 (10.7%)	0.546
Negative	42 (85.7%)	67 (89.3%)	

p/d – poorly differentiated; m/d – moderately differentiated; p-m/d – poorly-moderately differentiated; m-w/d – moderately-well differentiated; PD – progressive disease; PR – partial response; SD – stable disease; CTx – chemotherapy; CEA – carcinoembryonic antigen; CA199 – carbohydrate antigen 199; CA724 – carbohydrate antigen 724; LN – lymph node. # Cutoff value of CEA: 3.5 ng/ml; ## cutoff value of CA199: 30u/ml; * cutoff value of CA724: 8.2 u/ml.

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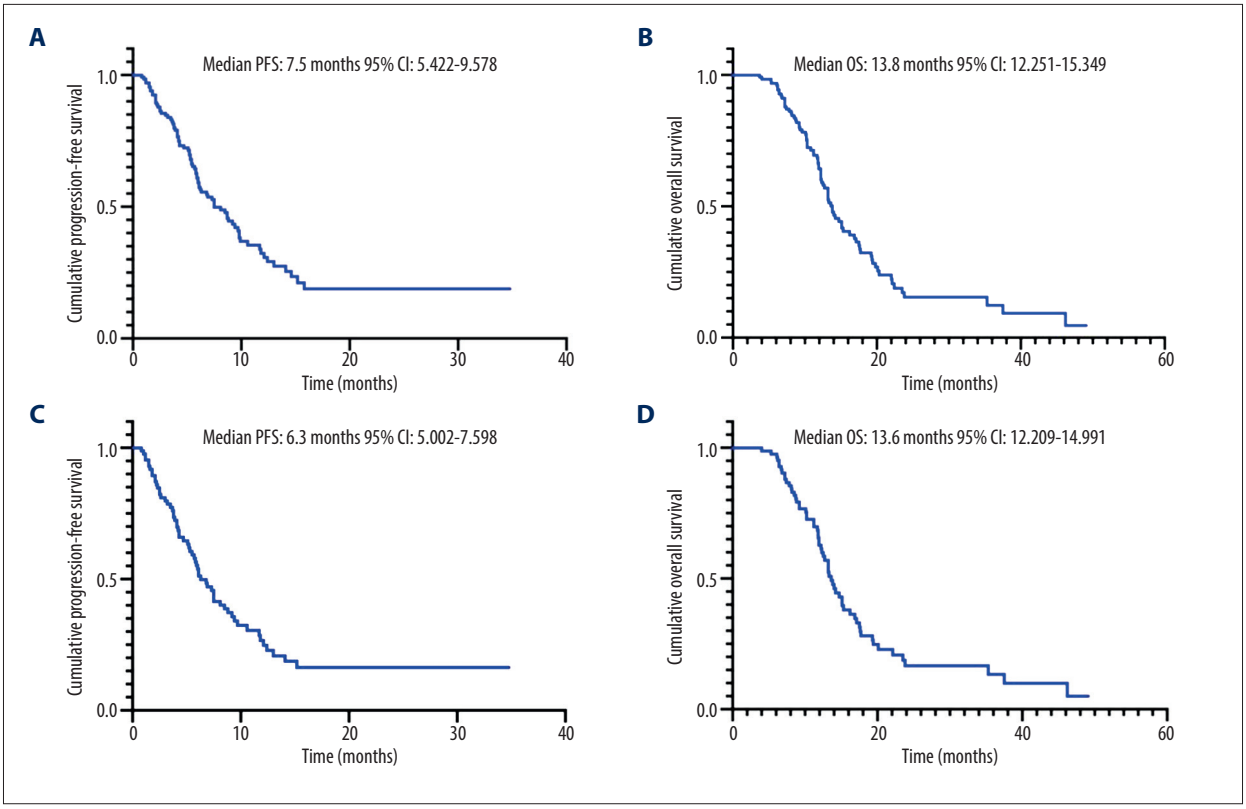

Figure 2. Kaplan-Meier curves for OS and PFS before and after matching. (**A**) PFS before matching, (**B**) OS before matching, (**C**) PFS after matching, (**D**) OS after matching PFS – progression-free survival; OS – overall survival.

Two groups of patients were categorized according to their pre-chemotherapy plasma D-dimer level (PDL): the low pretreatment D-dimer (LPD) group consisted of 89 patients with <1.5 ug/ml, and the high pretreatment D-dimer (HPD) group was composed of 45patients with PDL ≥1.5 ug/ml. A comparison of clinicopathologic variables was conducted between the 2 groups, as demonstrated in **Table 1**. Neither group had any statistically significant differences in sex, age, pathological diagnosis, tumor size, histology, or chemotherapy cycles. Patients in the LPD group were more likely to have malignancies situated in the upper third of the body (*P*=0.025) than in the HPD group. Among all patients, there was a median PFS of 7.5 months (with a 95% CI of 5.422-9.578) and a median OS of 13.8 months (with a 95% CI of 12.251-15.349). Kaplan-Meier curves for PFS and OS are shown in **Figure 2A, 2B**. None of the 134 patients achieved CR, 44 patients achieved PR, and 64 patients were SD. An objective response rate (ORR) of 32.84% and disease control rate (DCR) of 80.60% were achieved.

There was a significantly lower PFS and OS among HPD patients than among LPD patients (mPFS: 6.0 vs 8.7 months, *P*=0.015; mOS: 12.2 vs 15.1 months, *P*=0.037) (**Figures 3A, 4A, Table 2**). A survival analysis with univariate and multivariate variables is demonstrated in **Table 3**. The univariate analysis discovered a significant impact on OS for chemotherapy cycle, CA199, CA724, and D-dimer levels. Chemotherapy cycle and D-dimer levels independently predicted PFS through multivariate analysis. The chemotherapy cycle and CA724 levels were independently associated with survival. However, PDL was not significantly associated with OS (with a hazard ratio (HR) of 1.362, 95% CI of 0.851-2.181, *P*=0.198). The correlation between D-dimer levels and chemotherapy response before PSM is shown in **Table 4**. In accordance with the first response evaluation, patients with PD had an increased mean D-dimer by 1.72 ug/mL compared with patients with PR and SD (*P*=0.006). By contrast, the mean D-dimer increased by 1.21 mg/mL in 26 PD patients during the first response evaluation, although the difference was not statistically significant (*P*=0.113).

Patient Characteristics After Propensity Score Matching

A propensity score-based one-to-one matching method was used to select 43 patients for each group. As a result of the propensity score analysis, the characteristics are indicated in the right columns of **Table 5**. A total of 43 patients in the LPD were matched with 43 patients in the HPD as a result of covariate adjustment. In the matched study series, there was a median PFS of 6.3 months (with a 95% CI of 5.002-7.598) and a median OS of 13.6 months for all 89 patients (95% CI: 12.209-14.991). The Kaplan-Meier curve showing PFS and OS

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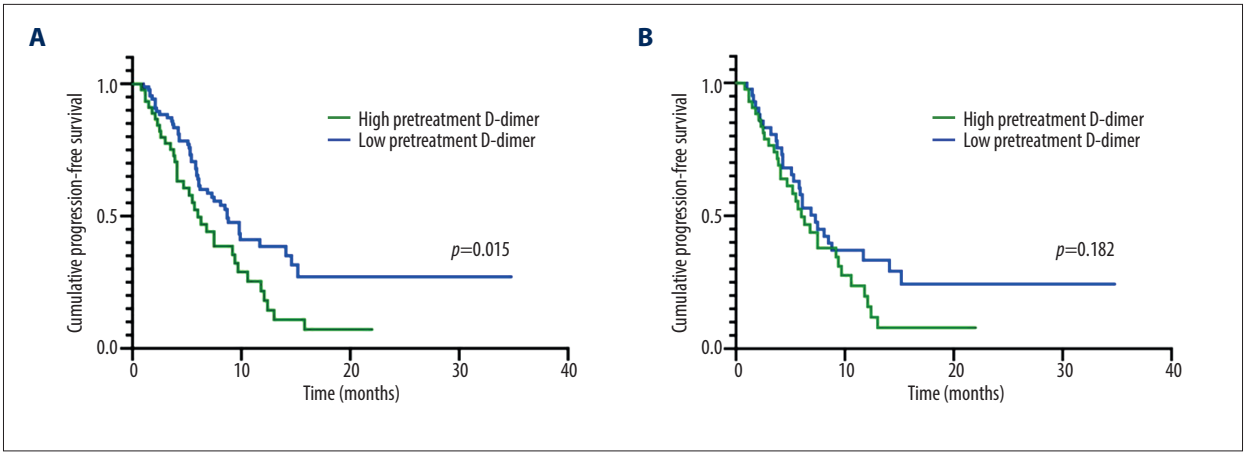

Figure 3. Kaplan-Meier curves for PFS before and after matching. (**A**) D-dimer PFS before matching. (**B**) D-dimer PFS after matching. PFS – progression-free survival.

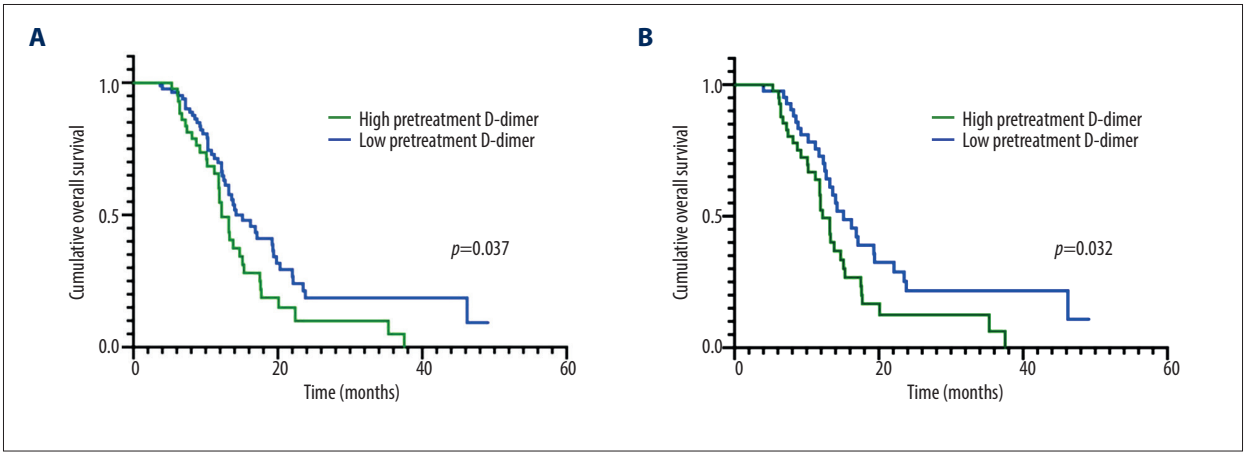

Figure 4. Kaplan-Meier curves for OS before and after matching. (**A**) D-dimer OS before matching. (**B**) D-dimer OS after matching. OS – overall survival.

is shown in **Figure 2C, 2D**. However, the OS time for LPD and HPD differed significantly. The OS of the HPD group was remarkably lower than in the LPD group (mOS: 12.2 vs 15.1 months, *P*=0.032) (**Table 6, Figure 4B**), but the PFS did not significantly vary between the 2 groups (mPFS: 6.0 vs 7.3 months, *P*=0.182) (**Figure 3B**). After PSM, only D-dimer levels (HR 1.746, 95% CI: 1.040-2.932; *P*=0.035) and chemotherapy cycle (HR 0.277, 95% CI: 0.160-0.478; *P*=0.000) showed significant associations with OS in univariate analysis. After the multivariate adjustment, the predictive value still existed (**Table 3**). As determined by multivariable survival analysis, D-dimer levels were independently associated with OS (HR 1.711, 95% CI 1.109-2.875; *P*=0.042) and chemotherapy cycle (HR 0.280, 95% CI 0.163-0.483; *P*=0.000). Other variables, including age, sex, pathological diagnosis, tumor location, tumor size, CEA, CA199, and CA724, showed no significant associations with PFS or OS after PSM (**Table 3**). The P values are calculated by Wilcoxon signed-rank test on the difference in D-dimer levels between at the pretreatment and the first response evaluation in **Table 4**. When PD patients were compared with PRs or SDs, their mean D-dimer increased by 1.91ug/mL (*P*=0.039). Conversely, 26 patients with PD had an increase in mean D-dimer of 2.21 mg/mL during the first response evaluation. However, statistical significance was not achieved by this difference (*P*=0.387). And AGC patients may benefit from the application of D-dimer levels as a predictor of chemotherapy response.

Discussion

This research was performed to determine whether plasma D-dimer levels can predict the PFS and OS of AGC patients. This is first as known research about the biomarker of D-dimer for AGC patients by an analysis of propensity score[15,16]. Before PSM, compared with HPD, patients in the LPD group had significantly longer median PFS and OS. After adjustment for covariates in PSM, however, only a better OS was observed in

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Table 2. Univariate analysis association of PFS and OS before a propensity score-matched analysis.

Variable	Cases	PFS (median, 95% CI)	P-value	OS (median, 95% CI)	P-value
Total patients	134	7.500 (5.422-9.578)		13.800 (12.251-15.349)	
Age##					
<60	53	6.000 (5.120-6.880)	0.371	12.700 (11.171-14.229)	0.358
≥60	81	8.700 (6.630-10.770)		14.200 (12.467-15.933)	
Sex##					
Male	99	7.500 (5.829-9.171)	0.755	14.200 (12.408-15.992)	0.787
Female	35	9.200 (4.238-14.162)		12.200 (10.710-13.690)	
Histology##					
p/d or p-m/d	68	6.200 (3.520-8.880)	0.810	12.700 (11.527-13.873)	0.750
m/d or m-w/d	5	7.500 (0.200-14.800)		11.900 (10.528-13.272)	
Pathological diagnosis##					
Adenocarcinoma	122	8.100 (5.834-10.366)	0.144	14.000 (12.337-15.663)	0.271
Signet-ring cell carcinoma	6	9.200		12.000 (9.960-14.440)	
Others	6	5.300 (2.938-7.662)		12.000 (6.618-17.782)	
Tumor location##					
Upper one-third	59	8.500 (6.752-10.248)	0.968	14.200 (12.114-16.286)	0.973
Middle one-third	40	6.100 (2.125-10.075)		13.600 (11.785-15.415)	
Lower one-third	33	7.500 (5.531-9.649)		11.900 (5.736-18.064)	
Whole	2	4.100		12.200	
Tumor size##					
<50 cm	127	7.500 (5.339-9.661)	0.918	13.600 (12.373-14.827)	0.318
≥50 cm	7	14.100 (0.000-29.678)		22.400 (11.458-33.342)	
Chemotherapy cycle##					
<8	59	6.100 (4.399-7.801)	0.015	10.100 (7.040-13.160)	0.000
≥8	75	8.700 (6.295-11.105)		17.500 (14.094-20.906)	
CEA*					
<3.5 ng/ml	54	8.700 (6.371-11.029)	0.385	14.000 (8.414-19.586)	0.224
≥3.5 ng/ml	76	7.500 (5.706-9.294)		13.300 (11.528-15.072)	
CA199*					
<30 u/ml	72	8.700 (6.880-10.520)	0.141	15.100 (13.302-16.898)	0.026
≥30 u/ml	58	6.000 (4.901-7.099)		12.200 (11.390-13.010)	
CA724*					
<8.2 u/ml	75	9.200 (7.839-10.561)	0.120	15.300 (10.121-20.479)	0.016
≥8.2 u/ml	53	5.900 (5.083-6.717)		12.500 (10.999-14.001)	
D-dimer					
<1.5 ug/ml	89	8.700 (6.565-10.835)	0.015	15.100 (11.728-18.472)	0.037
≥1.5 ug/ml	45	6.000 (4.177-7.823)		12.200 (10.876-13.524)	

PFS – progression-free survival; OS – overall survival; ** data available for 15 patients; * data available for 29 patients; # data available for 36 patients; ## data available for 54 patients.

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Table 3. Univariate and multivariate analysis association of PFS and OS before and after matching.

Variable	Pre-PSM (n=134)				Post-PSM (n=86)			
	Univariate analyses		Multivariate analyses		Univariate analyses		Multivariate analyses	
	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)
PFS								
Age	0.374	0.819 (0.526-1.273)			0.286	0.753 (0.447-1.269)		
Sex	0.756	0.924 (0.560-1.525)			0.511	0.812 (0.437-1.510)		
Histology	0.811	1.154 (0.357-3.728)			0.171	0.429 (0.128-1.441)		
Pathological diagnosis	0.108	1.449 (0.922-2.277)			0.204	1.555 (0.787-3.072)		
Tumor location	0.736	1.044 (0.812-1.344)			0.354	0.867 (0.642-1.172)		
Tumor size	0.919	1.048 (0.423-2.598)			0.511	1.407 (0.509-3.894)		
Chemotherapy cycle	0.016	0.572 (0.363-0.902)	0.036	0.611 (0.386-0.968)	0.050	0.596 (0.355-1.000)		
CEA	0.388	1.221 (0.776-1.923)			0.710	1.104 (0.654-1.865)		
CA199	0.144	1.392 (0.893-2.171)			0.136	1.477 (0.885-2.464)		
CA724	0.123	1.425 (0.908-2.236)			0.172	1.437 (0.854-2.418)		
D-dimer	0.017	1.711 (1.100-2.663)	0.038	1.603 (1.026-2.506)	0.186	1.412 (0.847-2.356)		
OS								
Age	0.361	0.813 (0.522-1.267)			0.610	0.872 (0.515-1.576)		
Sex	0.788	0.933 (0.563-1.546)			0.298	0.716 (0.381-1.343)		
Histology	0.753	1.208 (0.373-3.910)			0.416	0.602 (0.177-2.047)		
Pathological diagnosis	0.116	1.410 (0.919-2.166)			0.052	1.931 (0.994-3.752)		
Tumor location	0.937	1.010 (0.790-1.291)			0.794	0.961 (0.716-1.291)		
Tumor size	0.324	0.632 (0.253-1.574)			0.495	0.700 (0.252-1.947)		
Chemotherapy cycle	0.000	0.281 (0.175-0.449)	0.000	0.306 (0.188-0.497)	0.000	0.277 (0.160-0.478)	0.000	0.280 (0.163-0.483)
CEA	0.228	1.325 (0.838-2.095)			0.679	1.118 (0.658-1.901)		
CA199	0.028	1.654 (1.056-2.590)	0.204	1.360 (0.847-2.183)	0.083	1.578 (0.941-2.645)		
CA724	0.018	1.731 (1.097-2.730)	0.039	1.632 (1.025-2.600)	0.055	1.671 (0.989-2.824)		
D-dimer	0.040	1.595 (1.022-2.488)	0.198	1.362 (0.851-2.181)	0.035	1.746 (1.040-2.932)	0.042	1.711 (1.019-2.875)

PFS – progression-free survival; OS – overall survival.

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Table 4. Difference in D-dimer levels.

Response	Pre-PSM (n=134)			Post-PSM (n=86)		
	Pretreatment	At the first response evaluation	P#	Pretreatment	At the first response evaluation	P#
PR+SD	2.46±4.07	2.01±2.94	0.499	2.80±3.45	2.35±3.34	0.241
PD	2.52±3.82	3.73±5.43	0.113	3.05±4.22	4.26±6.00	0.387
P*	0.698	0.006		0.931	0.039	

PD – progressive disease; PR – partial response; SD – stable disease. The P # values are calculated by Wilcoxon signed-rank test on the difference in D-dimer levels between at the pretreatment and the first response evaluation. The P * values are calculated by Wilcoxon signed-rank test on the difference in D-dimer levels between at the response PD and PR+SD.

LPD (*P*=0.032). Although neither group had a significantly different PFS (*P*=0.182), it tended to be better in the LPD group and the survival benefits were clinical meaningful.

There is no doubt that CT scans and gastroscopies can improve the definitive diagnoses rate, but their diagnostic value is restricted by high costs, risk, and inconvenience. Noninvasive, sensitive, and specific biomarkers for advanced gastric malignancy would be beneficial given these limitations. Cancer patients often experience hypercoagulable states, which can put them at risk for thrombosis complications and can affect disease progression. As the smallest degradation product of plasmin on fibrin, the D-dimer exhibits unique characteristics. It is unclear what mechanisms are involved in the relationship between heightened plasma D-dimer levels and malignancy. Additionally, cancer cells quickly excite the coagulation system, damage the endothelial wall of the vascular system, and increase platelet and fibrinolytic activity [17]. A number of coagulation factors are linked to tumors, including fibrin, plasmin, and tissue factors. When tumor growth, metastasis, thrombosis, and angiogenesis occur, tumors internal microenvironment are dysregulated [18,19]. Aberrant activation of the coagulation-fibrinolysis system results from tissue factor, thrombin, and inflammatory factors released from tumor cells [20]. There are some proteins and cytokines secreted by tumor cells that disrupt the coagulation-fibrinolysis balance, and agglutinins and cytokines are released, damaging the endothelium of the vascular system [21]. Plasma D-dimer levels are elevated due to dysregulation in coagulation and with fibrinolysis. Coagulation abnormalities are common in cancer patients. The hypercoagulable state of patients with malignant tumors is considered to be related to tumor angiogenesis, growth, and dispersion, as well as metastatic cancer, ultimately leading to a poor prognosis. Consequently, AGC patients' plasma D-dimer levels before chemotherapy may be closely related to their prognosis.

Some malignancies, such as lung cancer, colorectal cancer and gastric cancer have been linked to poor prognosis when plasma D-dimer levels are high [22-26]. A mete-analysis by Xuelei Ma et al reported that the OS rate was 2.06, the 95% CI was 1.64-2.58 for lung cancer patients with higher D-dimer levels in 11 included studies [27]. The elevated pre-chemotherapy D-dimer levels shows the independent association with cancer mortality in advanced or recurrent cases [28]. According to researchers like Han-Yu Deng, high preoperative D-dimer levels may be an independent unfavorable prognostic factor in NSCLC patients who underwent surgery [29]. Our current results show that D-dimer level is a powerful prognostic indicator of OS in advanced AGC patients. To the best of our knowledge, this is the first study to explore whether plasma D-dimer levels are associated with OS time in the patients with advanced gastric cancer, and we found that OS was remarkably better in patients receiving LPD regimens than with HPD (*P*=0.032). After adjustment for confounders in PSM, there was a trend toward longer survival, but PFS was not significantly different (*P*=0.182),

CEA, CA199, and CA724 levels are not only closely related to gastrointestinal cancer, but are related to lung, uterine appendages, breast, and other malignant tumors outside the digestive tract. Therefore, they can be used as an auxiliary index to assist in diagnosis of malignant tumors, but the specificity is not high. Clinical use of combined D-dimer and tumor markers CEA, CA199, and CA724 can improve the sensitivity and specificity of cancer diagnosis, improve the diagnosis rate, effectively evaluate the treatment effect, and to a certain extent make up for the lack of a single marker for detection. Compared with other auxiliary examination methods, this combined method is simpler, faster, and less expensive, and combined D-dimer and tumor markers detection has important practical clinical value.

Some limitation should be considered in our research. First, owing to its retrospective nature, selection bias was inevitable, but PSM analysis was used to control for selection bias. Second, the sample size was small, which may have affected the statistical power. Third, patients with metastatic gastric cancer did not have their D-dimer measured as part of their baseline assessments. Affecting the conclusion of the present study of D-dimer patients before chemotherapy were not usually measured after

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Table 5. Baseline characteristics before matching and after matching.

Characteristics	Pre-PSM (n=134)			Post-PSM (n=86)		
	Low pretreatment D-dimer (<1.5 ug/ml, n=89)	High pretreatment D-dimer (≥1.5 ug/ml, n=45)	P	Low pretreatment D-Dimer (<1.5 ug/ml, n=43)	High pretreatment D-Dimer (≥1.5ug/ml, n=43)	P
Sex						
Male	70 (78.7%)	29 (64.4%)	0.077	36 (83.7%)	29 (67.4%)	0.079
Female	19 (21.3%)	16 (35.6%)		7 (16.3%)	14 (32.6%)	
Histology						
p/d or p-m/d	46 (95.8%)	22 (88.0%)	0.331	0	3 (13.0%)	0.243
m/d or m-w/d	2 (4.2%)	3 (12.0%)		18 (100.0%)	20 (87.0%)	
Age						
<60	34 (38.2%)	19 (42.2%)	0.653	14 (32.6%)	17 (39.5%)	0.500
≥60	55 (61.8%)	26 (57.8%)		29 (67.4%)	26 (60.5%)	
Pathological diagnosis						
Adenocarcinoma	81 (91.0%)	41 (91.1%)	0.495	42 (97.7%)	39 (90.7%)	0.241
Signet-ring cell carcinoma	3 (3.4%)	3 (6.7%)		0	3 (7.0%)	
Others	5 (5.6%)	1 (2.2%)		1 (2.3%)	1 (2.3%)	
Tumor location						
Upper one-third	44 (49.4%)	15 (33.3%)	0.025	15 (%)	15 (%)	1.000
Middle one-third	28 (31.5%)	12 (26.7%)		12 (%)	12 (%)	
Lower one-third	17 (19.1%)	16 (35.6%)		16 (%)	16 (%)	
Whole	0	2 (4.4%)		0	0	
Tumor size						
<50 cm	84 (94.4%)	43 (95.6%)	1.000	39 (90.7%)	42 (97.7%)	0.360
≥50 cm	5 (5.6%)	2 (4.4%)		4 (9.3%)	1 (2.3%)	
Best response						
PR	29 (32.6%)	15 (33.3%)	0.515	16 (37.2%)	14 (32.6%)	0.846
SD	45 (50.6%)	19 (42.2%)		18 (41.9%)	18 (41.9%)	
PD	15 (16.9%)	11 (24.4%)		9 (20.9%)	11 (25.6%)	
Chemotherapy cycles						
<8	38 (42.7%)	21 (46.7%)	0.662	19 (44.2%)	21 (48.8%)	0.665
≥8	51 (57.3%)	24 (53.3%)		24 (55.8%)	22 (51.2%)	
CEA						
<3.5 ng/ml	39 (44.8%)	15 (34.9%)	0.345	21 (48.8%)	13 (31.7%)	0.125
≥3.5 ng/ml	48 (55.2%)	28 (65.1%)		22 (51.2%)	28 (68.3%)	
CA199						
<30 u/ml	53 (60.9%)	19 (44.2%)	0.092	27 (62.8%)	17 (41.5%)	0.080
≥30 u/ml	34 (39.1%)	24 (55.8%)		16 (37.2%)	24 (58.5%)	
CA724						
<8.2 u/ml	54 (62.8%)	21 (50.0%)	0.185	27 (62.8%)	20 (50.0%)	0.273
≥8.2 u/ml	32 (37.2%)	21 (50.0%)		16 (37.2%)	20 (50.0%)	

Propensity matching factors are D-dimer concentration.

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Table 6. Univariate analysis association of PFS and OS after a propensity score-matched analysis.

Variable	Cases	PFS (median, 95% CI)	P-value	OS(median,95% CI)	P-value
Total patients	86	6.300 (5.002-7.598)		13.600 (12.209-14.991)	
Age##					
<60	31	5.200 (3.422-6.978)	0.283	13.200 (9.627-16.773)	0.608
≥60	55	7.500 (5.974-9.026)		14.200 (12.477-15.923)	
Sex##					
Male	65	6.800 (5.576-8.024)	0.509	13.800 (11.992-15.608)	0.294
Female	21	5.100 (0.000-13.427)		13.200 (10.462-15.938)	
Histology#					
p/d or p-m/d	38	6.000 (5.167-6.833)	0.156	12.700 (11.391-14.009)	0.406
m/d or m-w/d	3	7.500 (0.000-8.261)		11.900 (11.740-12.060)	
Pathological diagnosis##					
Adenocarcinoma	81	6.800 (5.481-8.119)	0.274	14.000 (12.320-15.680)	0.107
Signet-ring cell carcinoma	3	5.700		12.200	
Others	2	2.500		6.200	
Tumor location##					
Upper one-third	30	5.500 (2.191-8.809)	0.490	13.800 (12.034-15.566)	0.962
Middle one-third	24	6.100 (5.547-6.653)		13.600 (11.772-15.428)	
Lower one-third	32	7.500 (5.500-9.500)		11.900 (5.731-18.069)	
Whole	0				
Tumor size##					
<50 cm	81	6.800 (5.521-8.079)	0.507	13.600 (12.278-14.922)	0.491
≥50 cm	5	14.100 (0.250-7.550)		23.500 (5.094-41.906)	
Chemotherapy cycle##					
<8	40	5.800 (3.915-7.685)	0.047	10.100 (6.573-13.627)	0.000
≥8	46	7.500 (5.735-9.265)		17.100 (13.649-20.551)	
CEA*					
<3.5ng/ml	34	6.300 (4.146-8.454)	0.709	13.200 (11.245-15.155)	0.678
≥3.5ng/ml	50	6.100 (4.638-7.562)		13.600 (12.155-15.045)	
CA199*					
<30 u/ml	44	7.300 (4.888-9.712)	0.132	14.200 (12.551-15.849)	0.080
≥30u/ml	40	5.800 (4.690-6.910)		12.200 (11.177-13.223)	
CA724**					
<8.2 u/ml	47	7.500 (4.657-10.343)	0.168	15.100 (11.762-18.438)	0.051
≥8.2 u/ml	36	6.000 (4.789-7.211)		13.200 (11.233-15.167)	
D-dimer##					
<1.5 ug/ml	43	7.300 (5.383-9.217)	0.182	15.100 (11.350-18.850)	0.032
≥1.5 ug/ml	43	6.000 (4.231-7.769)		12.200 (10.671-13.729)	

PFS – progress-free survival; OS – overall survival. Data are available for 26 patients after a propensity score-matched analysis. Propensity matching factors are sex and tumor differentiation. ## Data available for 86 patients; * data available for 84 patients; ** data available for 83 patients; # data available for 41 patients.

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admission to hospital. Future studies should expand the sample size and conduct stratified analysis of each treatment regimen to reduce the possible impact of the treatment regimen on the results, thus providing more reliable conclusions. Our analysis only focused on the pre-chemotherapy value of the biomarker in patients with stage IV GC, and further validation is needed for patients with stage I-III GC. Despite these constraints, the findings of this study bring new evidence that D-dimer levels are predictive of prognosis in AGC patients before chemotherapy. CEA, CA199, CA724, and other biomarkers are universally available, can be measured quickly and easily, and do not require special equipment. Consequently, using D-dimers before chemotherapy is a low-cost, easy-to-implement method in clinical practice.

Limitations

The small sample size is a primary limitation, and the statistical power may therefore be affected. Affecting the conclusion of the present study of D-dimer patients before chemotherapy were not usually measured after admission to hospital. Owing to its retrospective nature, selection bias existed in this research inevitably. Few patients with metastatic gastric cancer did not have their D-dimer measured as part of their baseline assessments.

Conclusions

Plasma D-dimer analysis is an inexpensive, noninvasive, and simple method that can be a useful guide in predicting the dissemination and prognosis of advanced gastric cancer.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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