Japanese Journal of Gastroenterology and Hepatology

Research Article

ISSN: 2435-1210 | Volume 10

Elevated Pre-chemotherapy Plasma High D-dimer Levels Affect Survival of Advanced Gastric Cancer: An analysis of propensity score

Du Y[1], Jiang X[1], Fu K[1], Cui C[3*] and Luo S[2*]

[1]The Sixth Medical Center, Chinese PLA General Hospital, Department of Blood Transfusion, Beijing, China

[2]Department of GI Medical Oncology, Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China

[3]The Fourth Medical Center, Chinese PLA General Hospital, Department of Rehabilitation, Department of Orthopedic, Beijing, China

***Corresponding author:**

Chengwen Cui,

The Fourth Medical Center, Chinese PLA General Hospital, Department of Rehabilitation, Department of Orthopedic, Beijing, China

Suxia Luo,

Department of GI Medical Oncology, Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China

Received: 12 June 2023

Accepted: 04 Aug 2023

Published: 12 Aug 2023

J Short Name: JJGH

Citation:

Cui C, Luo S. Elevated Pre-chemotherapy Plasma High D-dimer Levels Affect Survival of Advanced Gastric Cancer: An analysis of propensity score. J Gastro Hepato. 2023; V10(1): 1-12

Keywords:

Advanced gastric cancer; D-dimer; Prognosis

1. Abstract

1.1. Background: Gastric cancer is a prevalent malignancy of the digestive system. There are presently no efficacious indicators to evaluate its curative effect and prognosis. Increased plasma D-dimer was researched to have a really deep connection between neoplasm in advanced stages and bad Overall Survival (OS) for some malignancies in distinct rates.

1.2. 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) during advanced gastric cancer (AGC) sufferers.

1.3. Results: 134 AGC were used to divide sufferers into two groups: the low pretreatment D-dimer (LPD) and the high pretreatment D-dimer (HPD) sufferers. Using propensity score analysis, one-to-one matches were performed for both groups to correct bias caused by different covariate distributions.Before matching, patients with HPD indicated a obviously lower median OS and PFS in contrast with LPD sufferers (months: 6.0 vs. 8.7, P=0.015;12.2 vs. 15.1, P=0.037), Whereas, the multivariate analysis indicated that as far as OS is concerned, PDL did not have an independent prognostic significance [with the hazard ratio (HR) of 1.362, 95% confidence interval (CI) of 0.851 to 2.181, P=0.198] and a multivariate analysis found chemotherapy cycles and CA724 to be independent prognostic factors against OS [with the HR of 0.306, 95% CI of 0.188 to 0.497, P=0.000 and the HR of 1.632, 95% CI of 1.025 to 2.600, P=0.039]. The first reponse evaluation's mean D-dimer of was raised by 1.72ug/mL in PD sufferers in comparison to PR and SD (P=0.006). There was a 15.1-month median OS for sufferers in the LPD compared to 12.2 months for those in the HPD (P=0.032). Additionally, the multivariate analysis discovered that OS was independently prognosticated by PDL [with the HR of 1.711, 95%CI of 1.019 to 2.875, P=0.042]. And the first reponse evaluations mean D-dimer was raised by 1.91ug/mL in patients with PD(P=0.039). 44 patients (32.84%) achieved partial response (PR), 64 (47.76%) achieved stable disease (SD), and 26(19.40%) had progressive disease (PD), attributing to an ORR of 32.84% and a DCR of 80.60%.

1.4. Conclusion: The high D-dimer level gastric cancer sufferers have worse outcomes.

2. Introduction

As a result of gastric cancer around 770,000 deaths occur each year, the fourth-leading reason of cancer-associated mortality around the world [1]. The advanced gastric cancer (AGC) has improved its 5-year overall survival (OS) rate from 23% to 45%, but the prognosis remains unsatisfactory [2-4].

For AGC, systemic chemotherapy is defined as a standard therapy. Whereas biomarkers for predicting or prognosticating gastric cancer are scarce. The main treatment option for AGC that cannot be resected is systemic chemotherapy. During the last decade, 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 and prognostic serum biomarkers for AGC than tissue-based biomarkers. In the past few decades, biomarkers have been explored to foresee the occurrence or OS of AGC.

Malignant tumor patients exhibit hypercoagulability as a physiological characteristic. It is essential for tumor angiogenesis that fibrin undergoes extracellular remodeling. D-Dimer is the result of tissue plasminogen activator degrading cross-linked fibrin factor XIIIa through generating plasmin from plasminogen. Through producing a monoclonal antibody that recognizes neither fibrinogen degradation nor noncross-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]. Sufferers (above 90%) with metastatic lesions showed abnormal clotting or fibrinolysis, containing antithrombin-III (AT-III) complexes fibinopeptides A (FPA) and D-dimer [7]. Cancer sufferers can easily prevent and treat venous thromboembolism (VTE), which is a conventionally overlooked cause of mortality and morbidity [8]. Specifically, there is a high risk of VTE intimately related to gastric cancer [9]. Blood flow stasis, endothelial damage, and hypercoagulability are all associated with VTE in cancer sufferers [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 DxDimer in AGC needs to be validated. The thrombin activatable fibrinolysis inhibitor (TAFI) and thrombin-antithrombin (TAT) complex levels [11], along with the stage IV sufferers' D-dimer levels, were increased in 52 gastric cancer sufferers during the lately research. One research involving 1178 sufferers beyond two years discovered that a subgroup of 50 gastric cancer sufferers 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. Latterly, researchers described that fact 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 affecting the extra-cellular matrix (ECM) [14].

No long-term research has examined the linkage exists in plasma D-dimer levels and OS in AGC sufferers. For the available research, we corrected the error due to different distributions of covariates by using both the cox proportional hazard regression and the propensity score method. The goal was for estimating how PDL may affect the prognosis of patients with AGC Our ultimate.

3. Materials and Methods

3.1. Patient Selection

Sufferers newly diagnosed with histologically substantiated advanced gastric malignancy therapied through chemotherapy at the Henan Cancer Hospital between January 2019 and December 2022 were identified from retrospective archival database of electronic records. They all suffer from metastatic gastric cancer and the tumor are all IV stage. The gastric cancer sufferers were appropriate for inclusion in this research as long as they fulfill the criteria: 1) age of the sufferer $\geq$ 18 years and with pathologically and/or computed tomography (CT) proven AGC; 2) prior palliative therapies (containing chemotherapy and radiotherapy) had not been administered to the patients; 3) patients were followed-up at least once. The following criteria were used to exclude participants from the study: 1) breastfeeding or pregnant women; 2) a previous malignancy was diagnosed, a concurrent malignancy was present, or secondary tumors were present in the sufferers; 3) some sufferers had medical histories associated with thromboembolism, familial coagulopathy, active infections, or disseminated intravascular coagulation; 4) both anticoagulant and antiaggregate therapies were administered to the sufferers; 5) missing data on PDL; 6) patients who underwent adjuvant chemotherapy after surgical resection are rejected.

3.2. Follow-up

The study enrolled 134 patients after excluding 16 patients as shown in Figure 1. In the control group, 89 sufferers with advanced gastric malignancy of low plasma D-dimer level. The data from both groups are summarized in Table 1. The research like this reviewed and sanctioned through the Ethics Committee of the Zhengzhou University Cancer Institute & Hospital. As a whole, 134 AGC patients at Affiliated Cancer Hospital of Zhengzhou University Cancer between January 2019 and Decemb- er 2022 were eligible for this study. Review of hospital records, conversance with sufferers' families, and reviews of the Henan Cancer Registry were used to obtain follow-up data for patients. Sufferers were detected till March 31, 2023. A person's OS time is the interval between when a gastric cancer was diagnosed and when it was last followed up or when it was fatal.

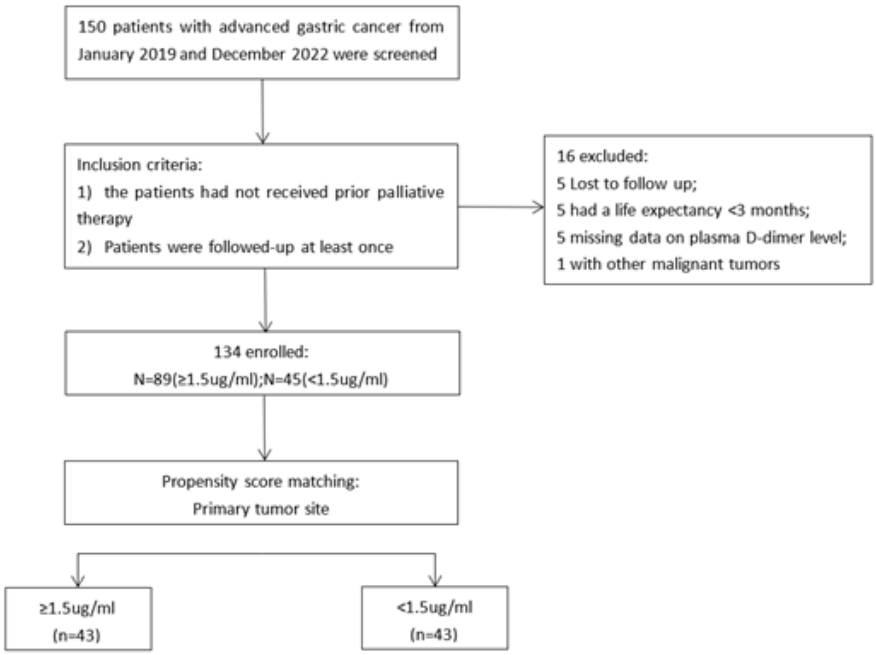

Figure 1: Trial profile

Table 1: Baseline Characteristics

	Low Pretreatment D-Dimer (＜1.5ug/ml,n = 89)	High Pretreatment D-Dimer (≥1.5ug/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			
<50cm	84 (94.4%)	43 (95.6%)	1
≥50cm	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: 3.5ng/ml, [※]Cutoff value of CA199: 30u/ml, *Cutoff value of CA724: 8.2u/ml.

3.3. Enzyme-linked Fluorescent Immunoassays for D-dimer Levels

Among advanced gastric malignancy sufferers undergoing chemotherapy or radiotherapy, venous blood samples were collected and enzyme-linked fluorescent immunoassays as well as miniVidas device (BioMeri-eux SA) were used to measure D-dimer levels. D-dimer levels beyond 1.5ug/ml were considered HPD.

3.4. Statistical Analyses

Comparing categorical data was done applying Chi-square tests or Fisher's exact tests. Contrasting continuous data with Student's t-tests or Mann-Whitney U tests. The survival benefit of those two treatments was contrasted applying Kaplan-Meier survival curves along with log-rank tests. Identifing prognostic factors, multivariate and univariate analyses applying Cox proportional hazard regression models were performed. Wilcoxon signed-rank test for paired sample comparison of nonparametric test. And an analysis of multivariate survival was conducted after univariate survival variables with P values>0.05 were incorporated. A hazard ratio (HR) along with corresponding 95% confidence interval (CI) were calculated for each predictor of survival. The significance level was considered to be a p-value of 0.05 (two-sided). Since sufferers were not assigned to LPD or HPD at random, we reduced selection bias and balanced potential confounders. Applying propensity score matching (PSM), sex, age, tumor location, tumor size, histology, pathological diagnosis, chemotherapy cycles, CEA, CA199, CA724 were all variables included in the propensity model. P<0.05 (bilateral) was deemed statistically valid. The propensity score indicates the conditional probability of a subject receiving a treatment given a vector of covariates and is often adopted 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 out through SPSS software, version 25.0 (IBM, Chicago, IL, USA).

4. Results

4.1. The Clinical and Pathopathological Features of the Entire Study Series Prior to Matching

At least 145 (96.7%) of the 150 sufferers were followed up no less than once. There were 134 patients included in the analysis after 16 patients were excluded. The follow-up was 12.0 months on average (range: 3-50) (Figure1). 134 patients included 99 males (73.9%) and 35 females (26.1%). The median age was 63, with a range of 29-79 years. The 26 patients of the 150 recruited sufferers 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, two cycles of chemotherapy had been finished. In conformity with Response Evaluation Criteria in Solid Tumors, version 1.1, computed tomography (CT) or magnetic resonance imaging was used to determine treatment response. The objective responses were classified as partial responses (PRs), stable diseases (SDs), and progressive diseases (PDs).

Two groups of sufferers were categorized according to their pre-chemotherapy plasma D-dimer level (PDL): the low pretreatment D-dimer (LPD) group, patients with<1.5ug/ml, including 89 patients; and the high pretreatment D-dimer (HPD) group, patients with PDL≥1.5ug/ml, including 45 patients. A comparison of clinicopathologic variables was conducted between the two groups, as demonstrated in Table 1. Both groups did not show any statistically notable differences in accordance with sex, age, pathological diagnosis, tumor size, histology, chemotherapy cycles, etc. While patients in the LPD were more likely to have malignancies situated in the upper third of the body (P=0.025) than in the HPD. Among all the research sufferers, there was a median PFS of 7.5 months (with a 95%CI of 5.422 to 9.578) and a median OS of 13.8 months (with a 95%CI of

12.251 to 15.349). Kaplan-Meier curves for PFS and OS were shown through Figure2A-B. In all 134 patients, no patient achieved CR, 44 patients achieved PR and 64 patients were SD. An ORR of 32.84% and 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.8.7months, P=0.015; mOS: 12.2 vs.15.1 months, P=0.037) (Figure 3A, Figure 4A, Table3). A survival analysis with univariate and multivariate variables is demonstrated in Table 5. 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 surviva. However, the PDL wasn't a remarkable factor for OS (with a hazard ratio (HR) of 1.362, 95% CI of 0.851 to 2.181, P=0.198). A correlation in D-dimer levels and chemotherapy response before PSM is shown in Table 6. In accordance with the first response evaluation, sufferers with PD had an increased mean D-dimer by 1.72 ug/mL compared with sufferers with PR and SD (P=0.006). By contrast, the mean D-dimer increased by 1.21 mg/mL in 26 PD sufferers during the first response evaluation, although no statistical significance was found in this difference (P = 0.113).

4.2. Sufferers 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 2. A total of 43 sufferers in the LPD were matched with 43 sufferers 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 to 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 was shown in Figure2C-2D. However, the OS time for LPD and HPD differed significantly. The HPD sufferers' OS were remarkablely lower than the LPD ones (mOS: 12.2 vs.15.1 months, P=0.032) (Table 4, Figure 4B), but the PFS didn't remarkably vary between the two 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 still existed (Table 5). As determined by multivariable survival analysis, D-dimer levels were independently associated with OS (with the HR of 1.711, 95%CI of 1.109 to 2.875; P=0.042) and chemotherapy cycle (with the HR of 0.280, 95%CI of 0.163 to 0.483; P=0.000). Other variables with age, gender, pathological diagnosis, tumor location, tumor size, CEA, CA199, CA724 included, showed no significant associations with PFS or OS after PSM (Table 5). After palliative treatment as determined by the changes in D-dimer levels the first response evaluation after PSM is presented in Table 6. 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 sufferers may benefit from the application of D-dimer levels as a predictor of chemotherapy response.

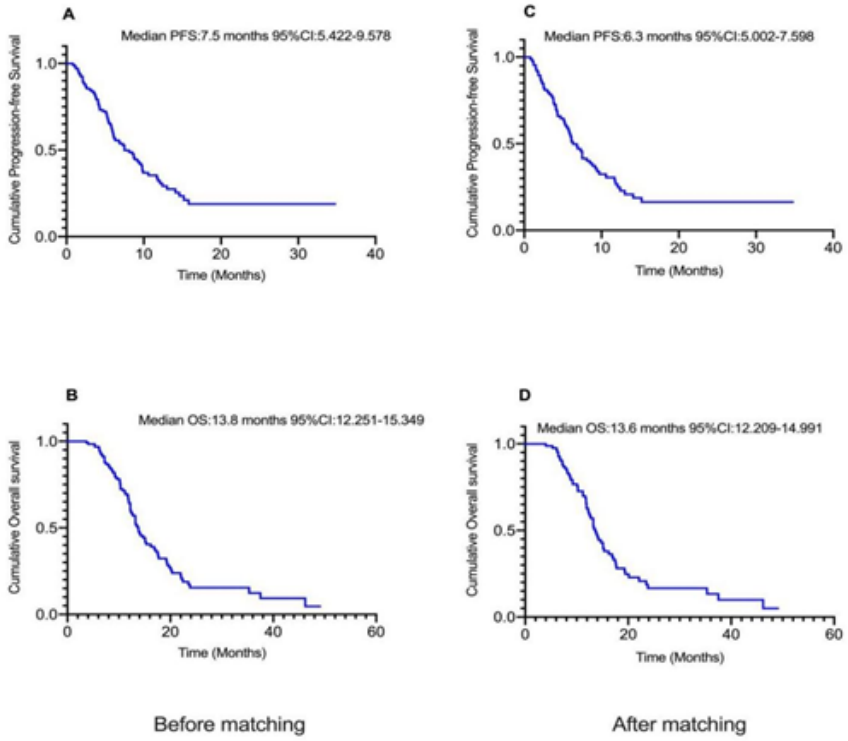

Figure 2: Kaplan-Meier curves for OS and PFS before and after matching

(A) PFS before matching. (B) OS before matching. (C) PFS after matching. (D) OS after matching.PFS= progression-free survival, OS=overall survival.

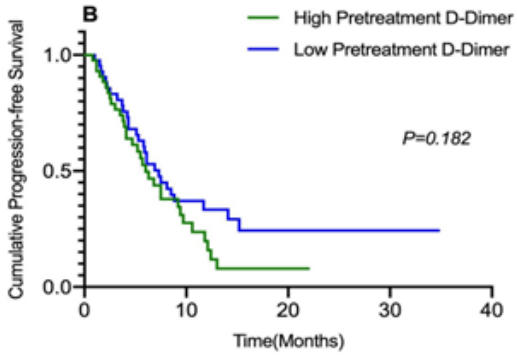

Figure 3: Kaplan-Meier curves for PFS before and after matching

(A)D-Dimer PFS before matching. (B)D-Dimer PFS after matching. PFS= progression-free survival.

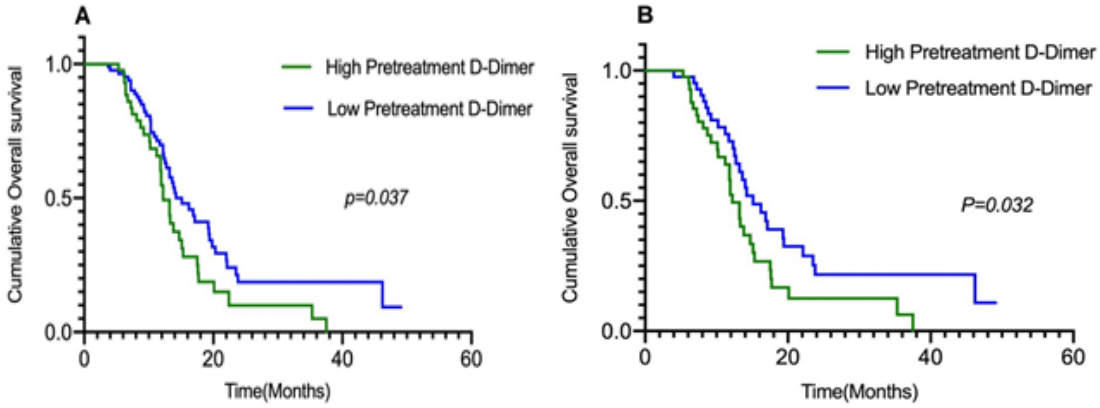

Figure 4: Kaplan-Meier curves for OS before and after matching

(A)D-Dimer OS before matching. (B)D-Dimer OS after matching. OS= overall survival.

Table 2: Baseline characteristics before matching and after matching

Characteristics	Pre-PSM (n=134)			Post-PSM（n=86）		
	Low Pretreatment D-Dimer (＜1.5ug/ml,n = 89)	High Pretreatment D-Dimer (≥1.5ug/ml,n = 45)	*P*	Low Pretreatment D-Dimer (＜1.5ug/ml,n = 43)	High Pretreatment D-Dimer (≥1.5ug/ml,n = 43)	*P*
Gender						
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%)	0.5
≥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
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						
＜50cm	84 (94.4%)	43 (95.6%)	1	39 (90.7%)	42 (97.7%)	0.36
≥50cm	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						
＜3.5ng/ml	39 (44.8%)	15 (34.9%)	0.345	21 (48.8%)	13 (31.7%)	0.125
≥3.5ng/ml	48 (55.2%)	28 (65.1%)		22 (51.2%)	28 (68.3%)	
CA199						
＜30u/ml	53 (60.9%)	19 (44.2%)	0.092	27 (62.8%)	17 (41.5%)	0.08
≥30u/ml	34 (39.1%)	24 (55.8%)		16 (37.2%)	24 (58.5%)	
CA724						
＜8.2u/ml	54 (62.8%)	21 (50.0%)	0.185	27 (62.8%)	20 (50.0%)	0.273
≥8.2u/ml	32 (37.2%)	21 (50.0%)		16 (37.2%)	20 (50.0%)	

Table 3: 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)	
Gender※					
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)	0.81	12.700(11.527-13.873)	0.75
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	9.2		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	4.1		12.2	

Tumor size※					
＜50cm	127	7.500(5.339-9.661)	0.918	13.600(12.373-14.827)	0.318
≥50cm	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
≥8	75	8.700(6.295-11.105)		17.500(14.094-20.906)	
CEA *					
＜3.5ng/ml	54	8.700(6.371-11.029)	0.385	14.000(8.414-19.586)	0.224
≥3.5ng/ml	76	7.500(5.706-9.294)		13.300(11.528-15.072)	
CA199 *					
＜30u/ml	72	8.700(6.880-10.520)	0.141	15.100(13.302-16.898)	0.026
≥30u/ml	58	6.000(4.901-7.099)		12.200(11.390-13.010)	
CA724 *					
＜8.2u/ml	75	9.200(7.839-10.561)	0.12	15.300(10.121-20.479)	0.016
≥8.2u/ml	53	5.900(5.083-6.717)		12.500(10.999-14.001)	
D-dimer					
＜1.5ug/ml	89	8.700(6.565-10.835)	0.015	15.100(11.728-18.472)	0.037
≥ 1.5ug/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.

Table 4: 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)	
Gender※					
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	5.7		12.2	
others	2	2.5		6.2	
Tumor location※					
upper one-third	30	5.500(2.191-8.809)	0.49	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※					
＜50cm	81	6.800(5.521-8.079)	0.507	13.600(12.278-14.922)	0.491
≥50cm	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
≥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*					
＜30u/ml	44	7.300(4.888-9.712)	0.132	14.200(12.551-15.849)	0.08
≥30u/ml	40	5.800(4.690-6.910)		12.200(11.177-13.223)	
CA724**					
＜8.2u/ml	47	7.500(4.657-10.343)	0.168	15.100(11.762-18.438)	0.051
≥8.2u/ml	36	6.000(4.789-7.211)		13.200(11.233-15.167)	
D-dimer ※					
＜1.5ug/ml	43	7.300(5.383-9.217)	0.182	15.100(11.350-18.850)	0.032
≥ 1.5ug/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 gender and tumor differentiation. ※Data available for 86 patients.*Data available for 84 patients. **Data available for 83 patients. #Data available for 41 patients.

Table 5: 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)		
Gender	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)	0.05	0.596(0.355-1.000)		
CEA	0.388	1.221(0.776-1.923)			0.71	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)			0.61	0.872(0.515-1.576)		
Gender	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	0.281(0.175-0.449)	0	0.306(0.188-0.497)	0	0.277(0.160-0.478)	0	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	0.04	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=Progress-free survival, OS=overall survival.

Table 6: Difference of D-Dimer Levels

	Pre-PSM(n=134)			Post-PSM(n=86)		
Response	Pretreatment	At the first reponse Evaluation	*P* #	Pretreatment	At the first reponse 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	

5. Discussion

The research was performed to make sure whether plasma D-dimer levels are able to prediction the PFS and OS of AGC patients. This is first as known to call into question about the biomarker of D-dimer for AGC sufferers. Before PSM, compared with HPD, patients in LPD had significantly longer median PFS and OS. After adjustment for covariates in PSM, however, only a better OS was observed in LPD (P=0.032). Although neither group had a significantly different PFS (P=0.182), it tended to be better in the LPD and the survival benefits were clinical meaningful.

There is no doubt that CT (computed tomography) scans and gastroscopies are able to both improve the definitive diagnoses rate, but their diagnostic value is restricted by expensive costs, risky situation, and inconvenienced conditions. The progression of 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 may have an impact on 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 relation between heightened plasma D-dimer levels and malignancy. Additionally, cancer cells excited the coagulation system straight away, damaged the endothelial wall of the vascular system, and raised platelet and fibrinolytic activity [15]. A number of coagulation factors are linked to tumors with fibrin, plasmin, and tissue factors included. When tumors grow, metastasize, thrombose, and angiogenesis occur, they are dysregulated [16-17]. An aberrant activation of the coagulation-fibrinolysis system results from tissue factor, thrombin, and inflammatory factors released from tumor cells [18]. There are some proteins and cytokines secreted by tumor cells that disrupt the coagulation-fibrinolysis balance, and agglutinins and cytokines are released, leading to injure to the endothelium of the vascular system [19]. Plasma D-dimer levels are elevated due to dysregulation in coagulation along with fibrinolysis. Coagulation abnormalities are commonly found 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 intimately related to their prognosis.

Some malignancy with lung cancer, colorectal cancer and gastric cancer included have been linked to poor prognoses when plasma D-dimer levels are high [20-24]. Xuelei Ma et al described that the OS rate was 2.06, the 95 % CI is from 1.64 to 2.58 for lung cancer sufferers with higher D-dimer levels across the 11 included studies [25]. The research demonstrated that the raised prechemotherapy D-dimer level shows the independent bearing on cancer mortality in advanced or recurrent cases [26]. According to researchers like Han-Yu Deng, high preoperative D-dimer levels may be an independent unfavorable prognostic factor in NSCLC sufferers with operative treatment [27]. According to our outcomes, the D-dimer level is a powerful prognostic indicator of OS through advanced AGC sufferers. It has never been studied whether plasma D-dimer levels related with OS time in the setting of advanced gastric tumor. During the research, OS was remarkably better in sufferers with LPD regimens than that with HPD (P=0.032). After adjustment for confounders in PSM, though the PFS didn't attain statistical significance (P=0.182), a trend towards prolonged survival was detected.

CEA, CA199, CA724 are not only closely related to gastrointestinal tumor, but also 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 the diagnosis of malignant tumors, but the specificity is not high. Clinical D-dimer and tumor markers CEA, CA199, CA724 combined detection can improve the sensitivity and specificity of tumor diagnosis, improve the diagnosis rate of tumor, effectively evaluate the treatment effect, to a certain extent, make up for the lack of single detection, and compared with other auxiliary examination methods more simple, fast, economic, D-dimer and tumor markers combined detection has important clinical practical value.

Of note, some limitation should be considered in our research. First, owing to its retrospective nature, selection bias existed in this research inevitably. However, the PSM analysis we carried out to control the selection bias. Second, the small sample size is a primary limitation, and the statistical power may be therefore affected. Third, as a result, sufferers with metastatic gastric cancer did not have their D-dimer measured as part of their baseline assessments. Additionally, the best treatment method is to expand the sample size, and conduct stratified analysis of each treatment regimen, so as to reduce the possible impact of the treatment regimen on the results, so as

to draw more reliable conclusions. Our analysis only focused on the pre-chemotherapy value of the biomarker in sufferers IV GC, and further validation is needed for patients I-III GC. Despite these constraints, the findings of this study bring an up-to-date perspective that the D-dimer levels are predictive of prognosis in AGC sufferers before chemotherapy. Besides, CEA, CA199, CA724 and other biomarkers are universally available, can be measured quickly and readily, and do not require special equipment. Consequently, using D-dimers before chemotherapy is a low-cost, easy-to-implement method in clinical practice.

6. Conclusions and Perspectives

The high D-dimer level gastric cancer sufferers have worse outcomes. However, D-dimer is not a necessary item for admission examination of patients with advanced gastric cancer, and the number of D-dimer patients examined before chemotherapy is limited. In this study of gastric cancer patients accept first-line chemotherapy scheme is not unified, but each curative effect is certainly different, although the difference is not obvious, whether the factor will affect the result is still no unity.In the future, we should expand the sample size to increase the reliability of our study.

7. Author Contributions

Yali Du: conceptualization, methodology, data visualization, manuscript drafting, and communication with journal editors. Chengwen Cui and Kaifei Fu: article screening, data analysis. Xuebing Jiang : article screening and manuscript review. Suxia Luo: manuscript review and editing, supervision, and project administration. All the authors have read and agreed to the published version of the manuscript.

8. Funding

Open Access funding enabled and organized by Major Military Scientific Research Project (No.AWS13J004).

9. Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

10. Consent for publication

Written informed consent was waived because all the information was de-identified.

11. Declaration of conflict of interest

All authors declare no conflict of interest.

References

1. Sung H, Ferlay J, Siegel RL. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71:209-249.
2. Xu W, Liu W, Wang L. Is D2 Lymphadenectomy Alone Suitable for Gastric Cancer with Bulky N2 and/or Para-Aortic Lymph Node Metastases After Preoperative Chemotherapy? Front Oncol. 2021; 11: 709617.
3. Noh SH, Park SR, Yang HK. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol. 2014; 15: 1389-96.
4. Ychou M, Boige V, Pignon JP. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocar- cinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011; 29: 1715-21.
5. Wen Y, Yang J, Han X. Fibrinogen-to-Albumin Ratio is Associated with All-Cause Mortality in Cancer Patients. Int J Gen Med. 2021; 14: 4867-4875.
6. Kim EY, Song KY. Prognostic value of D-dimer levels in patients with gastric cancer undergoing gastrectomy. Surg Oncol. 2021; 37: 101570.
7. Qiao W, Sha S, Song J. Association between multiple coagulation-related factors and lymph node metastasis in patients with gastric cancer: A retrospective cohort study. Front Oncol. 2023; 13: 1099857.
8. Zalunardo B, Panzavolta C, Bigolin P. Multidisciplinary Care for the Prevention and Treatment of Venous Thromboembolism in Patients with Cancer- Associated Thrombosis (CAT): Impact of Educational Interventions on CAT- Related Events and on Patients' and Clinicians' Awareness. Life (Basel). 2022; 12: 1594.
9. Yoshikawa T, Sano T, Terashima M. Incidence and risk factors for venous thromboembolism in the Cancer-VTE Registry stomach cancer subcohort. Gastric Cancer. 2023.
10. Wolberg AS, Aleman MM, Leiderman K. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. Anesth Analg. 2012; 114: 275-85.
11. Fidan E, Kavgaci H, Orem A. Thrombin activatable fibrinolysis inhibitor and thrombin-antithrombin-III-complex levels in patients with gastric cancer. Tumour Biol. 2012; 33: 1519-25.
12. Ay C, Dunkler D, Pirker R. High D-dimer levels are associated with poor prognosis in cancer patients. Haematologica. 2012; 97: 1158-64.
13. Zhang Q, Wu J, Bai X. Evaluation of Intra-Tumoral Vascularization in Hepatocellular Carcinomas. Front Med (Lausanne). 2020; 7: 584250.
14. Buller HR, van Doormaal FF, van Sluis GL. Cancer and thrombosis: from molecular mechanisms to clinical presentations. J Thromb Haemost. 2007; 5 Suppl 1: 246-54.
15. Siddiqui NA, Malik M, Wijeratne Fernando R. D-Dimer: A Potential Solution to Problems of Cancer Screening, Surveillance, and Prognosis Assessment. Cureus. 2021; 13: e15064.
16. De Bono JS, Harris JR, Burm SM. Systematic study of tissue factor expression in solid tumors. Cancer Rep (Hoboken). 2023; 6: e1699.
17. Sakurai M, Satoh T, Matsumoto K. High Pretreatment Plasma D-dimer Levels Are Associated With Poor Prognosis in Patients With Ovarian Cancer Independently of Venous Thromboembolism and Tumor Extension. Int J Gynecol Cancer. 2015; 25: 593-8.
18. Gil-Bernabé AM, Ferjancic S, Tlalka M. Recruitment of monocytes/macrophages by tissue factor-mediated coagulation is essential for metastatic cell survival and premetastatic niche establishment in mice. Blood. 2012; 119: 3164-75.
19. Zhang L, Wang Z, Xiao J, et al. Prognostic Value of Albumin to D-Dimer Ratio in Advanced Gastric Cancer. J Oncol. 2021; 2021: 9973743.

20. Ma M, Cao R, Wang W, et al. The D-dimer level predicts the prognosis in patients with lung cancer: a systematic review and meta-analysis. J Cardiothorac Surg. 2021; 16: 243.

21. Shibutani M, Kashiwagi S, Fukuoka T. The Significance of the D-Dimer Level as a Prognostic Marker for Survival and Treatment Outcomes in Patients With Stage IV Colorectal Cancer. In Vivo. 2023; 37: 440-444.

22. Li H, Sun L, Chen L. Effects of adiponectin, plasma D-dimer, inflammation and tumor markers on clinical characteristics and prognosis of patients with ovarian cancer. J Med Biochem. 2022; 41:71-78.

23. Zhang X, Wang X, Li W. D-dimer, a predictor of bad outcome in gastric cancer patients undergoing radical resection. Sci Rep. 2022; 12: 16432.

24. Kirwan CC, Descamps T, Castle J. Circulating tumour cells and hypercoagulability: a lethal relationship in metastatic breast cancer. Clin Transl Oncol. 2020; 22: 870- 877.

25. Ma X, Li Y, Zhang J. Prognostic role of D-dimer in patients with lung cancer: a meta-analysis. Tumour Biol. 2014; 35: 2103-9.

26. Yamamoto M, Yoshinaga K, Matsuyama A. Plasma D-dimer level as a mortality predictor in patients with advanced or recurrent colorectal cancer. Oncology. 2012; 83: 10-5.

27. Deng HY, Zheng X, Jiang R. Preoperative D-dimer level is an independent prognostic factor for non-small cell lung cancer after surgical resection: a systematic review and meta-analysis. Ann Transl Med. 2019; 7: 366.