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Preoperative D-dimer level and prognosis in patients diagnosed with gastric cancer and undergoing gastric cancer radical surgery: A retrospective cohort study

YUANZHENG ZHAO[1], JIAQI HAN[1], RONG YANG[2], SHUQIN WANG[1], KAI ZHANG[3] and HONGXIA LU[2]

[1]Department of Clinical Medicine, Fenyang College Shanxi Medical University, Lvliang, Shanxi 032200, P.R. China; [2]Department of Gastroenterology, Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, Shanxi 030013, P.R. China; [3]Department of Gastroenterology, Second Hospital of Jilin University, Changchun, Jilin 130000, P.R. China

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Abstract. Gastric cancer, one of the most aggressive tumors affecting the digestive tract, has seen a rise in both incidence and mortality rates in recent years, with a lack of clear prognostic indicators. D-dimer, a byproduct of fibrin degradation, is a conventional coagulation biomarker that has been investigated as a potential adverse prognostic factor for postoperative cancer patients. However, conflicting results exist, with some studies suggesting that D-dimer is an independent risk factor for the postoperative prognosis of gastric cancer, and others suggesting that there is no significant association between D-dimer level and gastric cancer prognosis. This controversy underscores the need for further research to determine the true influence of D-dimer level on the prognosis of postoperative cancer patients, including exploring the linear and non-linear associations, and identifying optimal critical values before surgery. The present study aimed to assess the association between preoperative D-dimer levels and 5-year overall survival (OS) rate in patients undergoing radical surgery for gastric cancer. Data was analyzed from patients diagnosed with gastric cancer who underwent a radical gastrectomy at Shanxi Cancer Hospital (Taiyuan, China) in 2017 and were followed up for 5 years until December 2022. Preoperative D-dimer levels and tumor-related indicators were collected as covariates from hospital records, with patient follow-up information obtained from the hospital's tracking system. Utilizing multivariate Cox regression, curve fitting and inflection point analysis, the present study sought to investigate the link between preoperative D-dimer levels and 5-year OS rate following radical surgery for gastric cancer. After strict admission and exclusion procedures, a total of 133 patients were included in the study and were then classified based on D-dimer level. Based on the mean value, the D-dimer levels were segregated into two distinct cohorts: The D-dimer_high group (n=66) and the D-dimer_low group (n=67). Cox multiple regression analysis was conducted using both continuous and binary variables. The results showed no effect in terms of the continuous variables, but higher preoperative D-dimer levels were significantly associated with a higher 5-year overall survival compared with lower preoperative D-dimer levels in the categorical variables. Therefore, curve fitting was performed, which indicated that the association between D-dimer level and 5-year survival rate after radical gastrectomy for cancer showed a U-shaped curve, with P<0.001, high and low D-dimer levels both indicated poorer prognosis. A curvilinear correlation was demonstrated between preoperative D-dimer levels and the 5-year survival rate following radical gastrectomy for cancer. Subsequently, an inflection point analysis found that the inflection point was located at 100-200 ng/ml. In conclusion, in patients undergoing radical gastrectomy for gastric cancer, preoperative D-dimer can be used to indicate the current state of the tumor to some extent through blood coagulation status. Notably, a U-shaped association exists between D-dimer levels and 5-year postoperative survival rate in gastric cancer. This association demonstrates varying effects across different intervals. Specifically, D-dimer levels <100 ng/ml are associated with a worse prognosis, whereas levels >200 ng/ml are associated with a better prognosis.

Correspondence to: Dr Hongxia Lu, Department of Gastroenterology, Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, 3 Zhigong New Street, Taiyuan, Shanxi 030013, P.R. China
E-mail: luhongxia@sxmu.edu.cn

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Introduction

Digestive tract cancers, including esophageal, gastric and colorectal cancer, are a type of prevalent malignant tumor, characterized by high mortality rates worldwide (1). As reported in the Global Cancer Statistics for 2020, there were 19.3 million new cases of cancer and 10 million deaths linked to the disease. Within these statistics, colorectal cancer has the third-highest incidence rate at 10%, while it is the second leading cause of cancer-related deaths at 9.4%. Gastric cancer, on the other hand, ranks fifth in incidence at 5.6% and fourth in mortality rate at 7.7% (2). According to the World Health Organization classification of tumors, tumors of the digestive system encompass several types of cancer, including esophageal, gastric, small intestinal, hepatocellular, gallbladder, cholangiocarcinoma, pancreatic and colorectal cancer (3). Gastrointestinal cancer exhibits one of the highest incidence and mortality rates among all types of cancer (4), and is a leading cause of cancer-related mortality (5). In addition, gastric cancer (GC) is a particularly aggressive type of malignancy, which originates from gastric mucosal epithelial cells (6). As one of the most prevalent malignant tumors of the digestive tract, GC is also characterized by a very high invasive capacity (7). Therefore, its incidence and mortality rates are very high worldwide, accounting for ~10% of all cancer-related deaths, thus posing a serious threat to global human health (8-12). Despite the decline in GC incidence and progress in the development of novel treatment approaches, the mortality rate among patients with GC remains high (13,14). Therefore, further methods for predicting prognosis and identifying novel biomarkers to improve patient outcomes are urgently needed.

D-dimer, a fibrin degradation product, serves as a conventional marker of clotting, with enhanced levels indicating a hypercoagulable state (15,16). Emerging evidence has suggested that tumor cells can release procoagulants or fibrinolytic substances, thus attracting platelets and promoting tumor progression via the excessive activation of coagulation (17-19). Previous studies demonstrated that heightened D-dimer levels were associated with a poor prognosis in several types of cancer including lung, colorectal, pancreatic cancer and gastric cancer, and more particularly in GC (20-22). Due to the visibility and convenience of measuring D-dimers, Guan *et al* (23) highlighted the significance of D-dimer monitoring in patients with cancer, including those with GC, as a reliable predictor of thromboembolism. Other studies further supported the association between high D-dimer levels and unfavorable outcomes in patients with GC (24-27). However, a propensity matching analysis performed by Liang *et al* (28) indicated that preoperative D-dimer elevation was not an independent prognostic factor for GC. Therefore, the present study aimed to investigate the association between preoperative D-dimer levels and long-term postoperative survival in patients with GC. To enhance the reliability of the findings, previous research was expanded upon (24-27) by incorporating additional covariates associated with prognosis and survival, such as smoking and drinking history, hypertension, diabetes, cardio-cerebral-renal diseases and immune-related markers specific to GC. Furthermore, non-linear associations, beyond the traditional linear analysis, were assessed. To evaluate the potential effect of the baseline characteristics of patients with GC on D-dimer prognostic assessments, patients who had undergone radical cancer surgery were randomly selected and their postoperative outcomes were assessed using a follow-up system. To minimize bias, the data were subjected to univariate and multivariate Cox regression analysis. A fitting curve was also conducted, and inflection point analysis was performed to determine the optimal cut off value.

Materials and methods

Study design. The target independent variable was preoperative D-dimer level obtained at baseline. The dependent variable was 5-year overall survival (OS) period (1=death; 0=survive).

Study population. The data from randomly selected patients with GC treated between January 24 and February 15, 2017 in Shanxi Province Cancer Hospital were collected. Most patients underwent surgery within 1 month of admission. To select patients who met the inclusion criteria, the authors had free access to their data. However, to ensure the privacy of the participants, following the establishment of the database, their names were immediately deleted. Therefore, no one, not even the authors, could ever identify each patient in the database. The inclusion criteria were as follows: i) Patients hospitalized in 2017; ii) who underwent radical treatment and R0 resection; iii) who were diagnosed with GC via postoperative pathological examination; iv) who had stage I-III disease, in accordance with the TNM staging system established by the American Joint Committee on Cancer (AJCC 7th ed., 2010) (29); and v) who were aged ≥18 years old. The exclusion criteria were the following: i) Patients who underwent major surgery within 6 months of the diagnosis; ii) who failed to undergo follow-up; iii) with first preoperative data in an external hospital; iv) with missing D-dimer levels and baseline data; v) with unspecified staging; vi) unspecified accumulation of nerves and vessels; vii) suffering from other types of cancer; viii) with severe liver and kidney injury; ix) with a history of preoperative neoadjuvant chemotherapy and x) pregnant or breastfeeding patients (Fig. 1).

Variables. The preoperative D-dimer levels were considered as the baseline levels. The first D-dimer levels (ng/ml) were measured and recorded after hospitalization. Based on the published guidelines and previous studies, the final outcome variables, such as 5-year OS rate, were assessed. Survival time was recorded in months. The selection criteria for confounding factors (covariates) were as follows: i) Demographic data; ii) variables reported in the previous literature that could affect preoperative D-dimer levels or 5-year OS rate; and iii) those based on clinical experience (age and smoking history, drinking history, hypertension history and diabetes history). Therefore, the following variables were used to construct the fully-adjusted model: i) Continuous variables, including age, and carbohydrate antigen (CA) 50, CA199, CA724, tissue polypeptide antigen and tumor-specific growth factor levels; and ii) categorical variables, including severe cardiovascular and cerebrovascular diseases, tumor site, Lauren classification, Tumor-Node-Metastasis (TNM) classification, staging invasion of vasculature and nerves, and postoperative neoadjuvant chemotherapy, in accordance with the TNM staging system established by the American Joint Committee on Cancer (AJCC 7th ed., 2010) (29) (Table I).

Follow-up procedure. Follow-up was conducted according to Shanxi Province Cancer Hospital's follow-up system. The follow-up period was 5 years, and the follow-up frequency is once a month. The cutoff date for follow-up was December 2022.

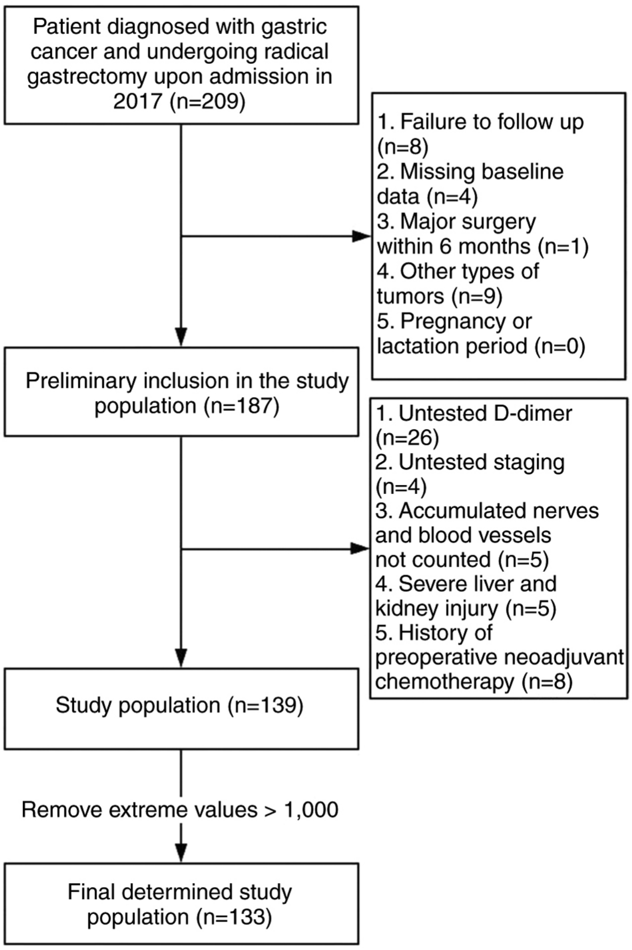

Figure 1. Process diagram for sample collection and arrangement of the research.

Statistical analysis. Mean value of the continuous variable D-dimer was used to generate a binary categorical variable (D-dimer_high and D-dimer_low groups. The remaining categorical variables are expressed as frequency or percentage. The differences between the D-dimer_high and D-dimer_low groups were compared using the χ^2 test for categorical variables, and the unpaired t-test and Mann-Whitney U test for continuous variables with normal and skewed distribution, respectively. Sensitivity analysis was performed to ensure the robustness of the data analysis. The continuous (D-dimer level) and binary (D-dimer_high and D-dimer_low) variables were assessed to verify the consistent significance of their effect values and identify potential non-linearity. In the multivariate analysis of the continuous variables, D-dimer levels were multiplied by 0.1 to enhance their significance (Table II). Therefore, univariate and multivariate Cox proportional hazard models were employed. A total of three models were constructed. Model 1, which was adjusted for age and diseases, model 2, which was adjusted for the variables of model 1 plus tumor-related description features, and model 3, which was adjusted for the variables of model 2 plus other influential covariates (Table III). To address the non-linearity of the preoperative D-dimer levels and 5-year OS rates, a generalized additive model and smooth curve fitting (penalized spline method) were performed (Fig. 2). When non-linearity was obtained, the inflection point was first calculated using a recursive algorithm, and a two-piecewise Cox proportional hazard model on both sides of the inflection point was then constructed (Table IV). Furthermore, to more intuitively display the curve association of its existence, Kaplan-Meier (K-M) survival curves at the 2nd and 5th percentiles were plotted, the cutting standards were a mean of 2 and 5 equal parts, respectively (Figs. 3 and 4). All analyses were performed using R Statistical Software (http://www.R-project.org, The R Foundation) and Free Statistics analysis platform (FreeClinical Medical Technology Co., Ltd.). A two-tailed test was performed and P<0.05 was considered to indicate a statistically significant difference. Due to missing values in some covariates, to analyze the data more accurately without adding new ones or reducing sample size, the dummy variable imputation method was applied.

Results

Baseline characteristics of the selected participants. A total of 133 participants were included in the final data analysis (Fig. 1). The baseline characteristics of participants allocated to the D-dimer_high and D-dimer_low groups are listed in Table I. The mean age of the selected participants was 60.3±9.2 years (range, 34-85 years old, with 78.9% being male. To ensure consistency in the high group and result stability, due to the limited sample size, extreme values of >1,000 ng/ml were excluded.

Univariate analysis. The results of the univariate analysis are shown in Table II. The preliminary results revealed that the effect value of D-dimer levels as a binary variable was significantly greater compared with that obtained from D-dimer levels as a continuous variable. The aforementioned preliminary findings suggested that there was a curved association between these variables. In the current analysis, as many and appropriate covariates as possible were included in the multi-model and multi-factor analysis (Tables I and II). Covariates included in Cox multivariate analysis and curve fitting were determined as age, presence of disease, site, Lauren classification, T stage, N stage, stating, nerve involvement, vessel involvement, postoperative chemotherapy, TPA, CA50, CA199, CA724 and TSGF.

Multi-model and multi-factor analysis. In the present study, three models were constructed to analyze the independent effects of preoperative D-dimer levels on the 5-year OS rate using a multivariate Cox proportional hazard model. The effect sizes [hazard ratio (HR) and 95% confidence interval (CI)] of D-dimer levels as a binary and continuous variable in each model are listed in Table III. In model 1, when D-dimer levels served as a continuous variable, the effect size indicated that a one-unit change in preoperative D-dimer levels was associated with the risk of death. Conversely, when D-dimer levels were used as a binary variable, the effect size suggested that there was an increased risk of mortality in the D-dimer_High group compared with the D-dimer_Low group. For example, the effect size of the 5-year OS rate in model 1 (D-dimer levels, continuous variable) showed that a one-unit change in preoperative D-dimer levels was associated with a change in

Table I. Baseline data of variables.

Variables	Total (n=133)	D-dimer_low (n=66)	D-dimer_high (n=67)	P-value
Mean age ± SD, years	60.3±9.2	57.4±9.1	63.1±8.5	<0.001
Sex				0.037
Female	28 (21.1)	9 (13.6)	19 (28.4)	
Male	105 (78.9)	57 (86.4)	48 (71.6)	
Smoking status				0.099
Non-smoker	76 (57.1)	33 (50.0)	43 (64.2)	
Smoker	57 (42.9)	33 (50.0)	24 (35.8)	
Hypertension				0.446
Presence	101 (75.9)	52 (78.8)	49 (73.1)	
Absence	32 (24.1)	14 (21.2)	18 (26.9)	
Diseases				0.037
Presence	105 (78.9)	57 (86.4)	48 (71.6)	
Absence	28 (21.1)	9 (13.6)	19 (28.4)	
Site				0.778
Proximal	75 (56.4)	36 (54.5)	39 (58.2)	
Gastric body	25 (18.8)	14 (21.2)	11 (16.4)	
Distal	33 (24.8)	16 (24.2)	17 (25.4)	
Lauren classification				0.336
Intestinal	16 (28.6)	9 (33.3)	7 (24.1)	
Diffuse	20 (35.7)	11 (40.7)	9 (31.0)	
Mixed type	20 (35.7)	7 (25.9)	13 (44.8)	
T stage				0.037
T1	15 (11.3)	9 (13.6)	6 (9.0)	
T2	12 (9.0)	10 (15.2)	2 (3.0)	
T3	40 (30.1)	15 (22.7)	25 (37.3)	
T4	66 (49.6)	32 (48.5)	34 (50.7)	
N stage				0.012
N0	38 (28.6)	22 (33.3)	16 (23.9)	
N1	28 (21.1)	17 (25.8)	11 (16.4)	
N2	25 (18.8)	15 (22.7)	10 (14.9)	
N3	42 (31.6)	12 (18.2)	30 (44.8)	
TNM stage				0.07
I	14 (10.5)	11 (16.7)	3 (4.5)	
II	44 (33.1)	21 (31.8)	23 (34.3)	
III	75 (56.4)	34 (51.5)	41 (61.2)	
Nerve involvement				0.186
Negative	75 (56.4)	41 (62.1)	34 (50.7)	
Positive	58 (43.6)	25 (37.9)	33 (49.3)	
Vessel involvement				0.323
Negative	79 (59.4)	42 (63.6)	37 (55.2)	
Positive	54 (40.6)	24 (36.4)	30 (44.8)	
Postoperative chemotherapy				0.068
Negative	65 (48.9)	27 (40.9)	38 (56.7)	
Positive	68 (51.1)	39 (59.1)	29 (43.3)	
Antithrombin-III, %	106.7±14.5	107.0±14.1	106.4±14.9	0.806
HER-2				0.265
Negative	51 (86.4)	20 (80.0)	31 (91.2)	
Positive	8 (13.6)	5 (20.0)	3 (8.8)	
TSGF (pg/ml)	60.0±7.5	57.4±5.6	62.1±8.1	0.002
VEGF (pg/ml)	468.4±333.3	402.2±281.6	532.1±370.6	0.166

Table I. Continued.

Variables	Total (n=133)	D-dimer_low (n=66)	D-dimer_high (n=67)	P-value
sIL-2R (U/ml)	334.8±80.8	331.9±87.4	337.2±75.7	0.759
AFP (ug/l)	4.6±13.7	6.7±19.6	2.6±2.2	0.123
CEA (ug/l)	5.2±12.7	3.7±10.5	6.7±14.5	0.186
CA242, U/ml)	25.8±58.8	15.9±35.7	35.6±74.2	0.063
CA724 (U/ml)	10.0±24.7	5.6±11.2	14.4±32.7	0.046
CA50 (U/ml)	2.6±6.5	1.2±1.7	3.9±8.8	0.043
CA199 (U/ml)	42.7±72.9	29.9±46.4	55.8±90.9	0.048
TPS (U/l)	107.6±84.7	112.3±92.9	103.1±76.7	0.59
TPA (ng/ml)	1.0±3.7	0.6±1.2	1.3±5.1	0.357
5-year OS				0.011
Survival	72 (54.1)	43 (65.2)	29 (43.3)	
Death	61 (45.9)	23 (34.8)	38 (56.7)	

TSGF, tumor supplied group of factors; VEGF, Vascular Endothelial Growth Factor; slL-2R, Soluble interleukin-2 receptor; AFP, Alpha-fetoprotein; CEA, Carcinoembryonic Antigen; CA199, Carbohydrate Antigen 199; TPS, Tissue Polypeptide Specific antigen; TPA, Tissue Polypeptide Antigen. Some data were missing for Lauren classification and HER-2.

the risk of death (HR=1.01; 95% CI, 1.00-1.03), however this was not significant. Similarly, the effect size of the 5-year OS rate in model 1 (D-dimer levels, binary variable) revealed an association between the mortality risk and D-dimer levels (low and high D-dimer groups; HR=1.74; 95 CI, 1.00-3.01). In model 2, when D-dimer levels served as a continuous variable, a one-unit increase in preoperative D-dimer levels was associated with an increased mortality risk (HR=1.01; 95% CI, 1.00-1.03), however this was not significant. On the other hand, when D-dimer levels served as binary variable in the same model, a greater mortality risk was obtained in the D-dimer_high group compared with the D-dimer_low group (HR=1.67; 95% CI, 0.93-2.98), however this was not significant. In the fully adjusted model, which was adjusted for as many covariates as possible within an appropriate range (model 3), there was no statistical significance in the linear associations among the different covariates.

Non-linearity of preoperative D-dimer levels and 5-year OS rate. In the present study, the non-linear association between preoperative D-dimer levels and 5-year OS rate was also assessed (Fig. 2). The smooth curve and the results from the Generalized Additive Model revealed a non-linear association between preoperative D-dimer levels and 5-year OS rate, even after adjusting for different variables, such as sex, diseases, tumor site, T stage, N stage, TNM staging, Lauren classification, nerve involvement, vessel involvement, postoperative chemotherapy and various tumor markers. Both a Cox proportional hazard model and a two-piecewise Cox proportional hazard model were utilized to analyze the association. The best model was selected based on the P-value of the log likelihood-ratio test. As P-value of <0.05 was obtained, the two-piecewise Cox proportional hazard model was selected. This model could more accurately capture the association. From Fig. 2, it can be observed that there is a U-shaped curve association between preoperative D-dimer levels and prognosis of gastric cancer. Both excessively high and low levels of D-dimer suggest lower 5-year survival rates in patients, further indicating a poor prognosis for gastric cancer. Through this model and a recursive algorithm, an inflection point of 110.449 was calculated. The effect size on the left and right sides of the inflection point was 0.451 and 1.0036, respectively (Table IV).

K-M survival curves. To represent the association between D-dimer levels and survival, K-M survival curves were plotted by dividing distribution at two and five equal parts. K-M survival curve indicated that the survival time was longer in the D-dimer_high group compared with that in the D-dimer_low group. This finding was consistent with that reported in a previous study (27). However, D-dimer_lowest group ranked third in D-dimer survival, thus clearly supporting the presence of a curved association (Figs. 3 and 4).

Discussion

It is widely accepted that several factors can affect the association between D-dimer levels and GC prognosis. Therefore, the results have always been controversial. Based on the risk of biases, in the present study, several measures were taken to obtain more rigorous results. The preoperative D-dimer levels, at initial admission, were considered as the baseline levels. Therefore, to avoid the effect of different surgical methods and types on D-dimer levels, these levels were not determined postoperatively. Regarding the research methodology, multiple factor and multiple model regression analyses were performed by incorporating as many covariates as possible. Therefore, the presence of similar results among different models was verified.

The results of the current study revealed a positive association between preoperative D-dimer levels and 5-year OS rate, even after adjusting for other covariates. Therefore, it was hypothesized that preoperative D-dimer

Table II. Cox single factor regression analysis.

Variables	HR (95% CI)	P-value
D-dimer*0.1 (cont. var.)	1.02 (1.00-1.03)	0.017
D-dimer_cut: High vs. Low	2.07 (1.23-3.48)	0.006
Age	1.04 (1.01-1.07)	0.017
Sex: Male vs. female	1.12 (0.59-2.10)	0.734
Smoking status: Smoker vs. non-smoker	0.65 (0.38-1.10)	0.108
Hypertension: Presence vs. absence	1.32 (0.76-2.29)	0.326
Diseases: Presence vs. absence	1.50 (0.85-2.62)	0.159
Site		0.992
Proximal	Reference	
Gastric body	0.96 (0.49-1.88)	0.898
Distal	0.99 (0.54-1.81)	0.972
Lauren classification		0.147
Intestinal	Reference	
Diffuse	0.39 (0.15-1.02)	0.054
Mixed type	0.61 (0.26-1.44)	0.26
T stage		0.008
T1	Reference	
T2	1.36 (0.27-6.75)	0.705
T3	2.18 (0.63-7.47)	0.217
T4	3.96 (1.22-12.84)	0.022
N stage		<0.001
N0	Reference	
N1	1.43 (0.54-3.80)	0.478
N2	3.29 (1.38-7.85)	0.007
N3	5.81 (2.66-12.69)	<0.001
TNM stage		<0.001
I	Reference	
II	2.57 (0.59-11.25)	0.210
III	5.55 (1.35-22.93)	0.018
Nerve: Invasion vs. not	2.65 (1.59-4.42)	<0.001
Vessel: Invasion vs. not	2.78 (1.66-4.64)	<0.001
Postoperative chemotherapy: Treatment vs. not	0.72 (0.43-1.19)	0.200
Antithrombin III	0.99 (0.97-1.01)	0.390
HER2: 1 vs. 0	0.97 (0.37-2.51)	0.943
TSGF	1.02 (0.98-1.06)	0.285
VEGF	1.00 (0.99-1.00)	0.566
sIL2R	0.99 (0.99-1.00)	0.079
AFP	0.99 (0.97-1.02)	0.737
CEA	1.01 (0.99-1.02)	0.205
CA242	1.00 (0.99-1.01)	0.156
CA72.4	1.01 (1.00-1.02)	0.072
CA50	1.03 (1.00-1.05)	0.058
CA199	1.00 (0.99-1.01)	0.087
TPS	1.00 (0.99-1.00)	0.954
TPA	1.10 (1.03-1.17)	0.003

HR, hazard ratio; CI, confidence interval. TSGF, Tumor Supplied Group of Factors; VEGF, Vascular Endothelial Growth Factor; sIL-2R, Soluble interleukin-2 receptor; AFP, Alpha-fetoprotein; CEA, Carcinoembryonic Antigen; CA199, Carbohydrate Antigen 199; TPS, Tissue Polypeptide Specific antigen; TPA, Tissue Polypeptide Antigen.

levels could exploit the strong invasive capacity of GC and its susceptibility to metastasis, thus further suggesting that blood D-dimer levels could predict tumor status. Notably, the results also showed that the effect sizes on the left and right sides of the inflection point were not consistent [left, 0.451 (0.429-0.474); right, 1.0036 (0.9967-1.0105)]. The aforementioned findings indicated a U-shaped independent association between preoperative D-dimer levels and 5-year OS rate. Therefore, different effects were obtained in different intervals. More particularly, preoperative D-dimer levels of <100 ng/ml and >200 ng/ml were associated with worse and better prognosis in GC, respectively. The aforementioned results not only indicated that preoperative D-dimer levels were an independent risk factor for GC prognosis within a specific interval, but also supported that the malignant status of a tumor could not simply directly associated with the coagulation status of the blood, since low D-dimer levels were also associated with poor tumor prognosis. In fact, this finding is also consistent with the clinical work experience, since patients with GC commonly first experience hypercoagulability, followed by hypocoagulability and bleeding. This observation further suggested that in patients with GC, preoperative D-dimer levels could not be necessarily lower compared with those in healthy patients. According to existing confirmed tumor physiology, patients with advanced gastric cancer typically experience more severe tumor infiltration depth and vascular invasion, which may form cancer emboli and further lead to hypercoagulable blood (30-32). However, the low coagulation state that occurs after high blood coagulation cannot be explained by existing research. We speculate that this may be due to the long-term hypercoagulability of blood in late-stage tumors, which leads to a large consumption of platelets and procoagulant factors. By contrast, anticoagulant factors will increase compensatorily, causing the blood to gradually transition from hypercoagulability to hypercoagulability. Therefore, in clinical practice, further decisions should be made based on a comprehensive evaluation of the actual staging of the tumor, and vigilance should be maintained in the face of low coagulation after high coagulation in patients. Once the risk of bleeding is detected, timely rescue measures should be taken. Overall, the results of the current study demonstrated that the malignancy of GC was not directly associated with the coagulation status of the blood, but it could also be associated with other factors involved. For example, changes in procoagulant and anticoagulant factors caused by long-term hypercoagulability in the blood. Therefore, the malignancy of gastric cancer cannot be directly inferred based on blood hypercoagulability, and low coagulation status may also predict poor prognosis.

Kim and Song (27) suggested that high D-dimer levels immediately after surgery were significantly associated with advanced T and TNM stages (P=0.001 and P=0.006, respectively). Patients in the high D-dimer levels group displayed significantly lower overall and disease-free survival rate compared with those in the low D-dimer levels group. The aforementioned association was evident in the D-dimer levels before surgery, immediately after surgery, on postoperative day 1 and on postoperative day 30. The multivariate analysis, adjusted only for TNM stage and cure rate, in a sample of

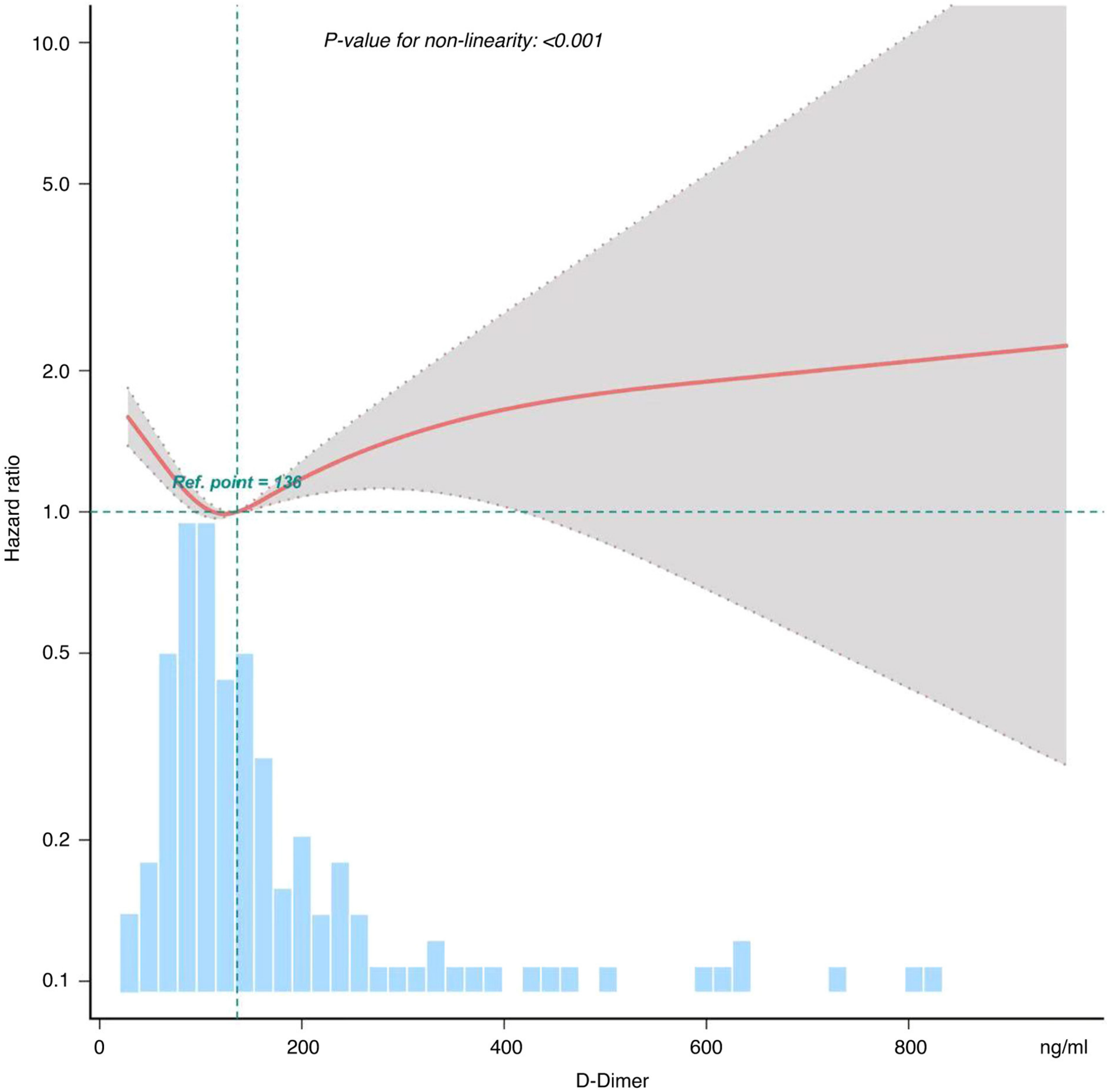

Figure 2. Curve fitting. Blue, sample distribution; red line represents the effect value, and the red shadow represents the confidence interval.

666 participants, identified immediate postoperative D-dimer levels as an independent prognostic factor for OS (HR, 2.52; P=0.010). The research results by Kim and Song (27) were not completely consistent with the results of the current study. Therefore, in the present study, the multivariate analysis was only adjusted for TNM staging (Table V) and the results were consistent with those of the study by Kim and Song (27). The results of the current study were also consistent with other previous studies; however, without a clear linear association.

Liang *et al* (28) reported that patients with GC and increased D-dimer levels (EG group) were more likely to have tumors with a size of ≥5 cm (67.5 vs. 55.8%; P=0.006), an increased average age (64.0±10.8 vs. 60.5±11.6 years; P<0.001) and advanced T, N and TNM stages, compared with patients with normal D-dimer levels (NG group). In addition, the 5-year OS of patients with elevated D-dimer levels was significantly lower than that in patients with normal levels (27.0 vs. 42.6%; P<0.001), thus indicating that D-dimer levels were not an independent prognostic factor for OS in the multivariate analysis (HR=1.13; 95% CI, 0.92-1.39; P=0.236). After matching, 163 patients in the EG and NG groups with the same characteristics were selected. The 5-year OS rate for patients in the EG group was 27.0% compared with 25.8% recorded for patients in the NG group (P=0.809). This finding was consistent with that obtained in the multi-model and multi-factor analysis of the present study, where the D-dimer levels served as a continuous variable. However, the abovementioned study mainly focused on exploring linear associations and not non-linear ones. Furthermore, the study by Liang *et al* (28) set the threshold for distinguishing patients with high D-dimer

Table III. Cox multivariate regression analysis.

A, D-dimer levels as binary variables

Model	Variable	Total patients, n	Events, n (%)	Follow-up time, days	Crude HR (95% CI)	Crude P-value	Adjusted HR (95% CI)	Adjusted P-value
Model 1	D-dimer_low	66	23 (34.8)	3,166	1 (Reference)		1 (Reference)	
	D-dimer_high	67	38 (56.7)	2,405	2.07 (1.23-3.48)	0.006	1.74 (1.00-3.01)	0.048
Model 2	D-dimer_low	66	23 (34.8)	3,166	1 (Reference)		1 (Reference)	
	D-dimer_high	67	38 (56.7)	2,405	2.07 (1.23-3.48)	0.006	1.67 (0.93-2.98)	0.083
Model 3	D-dimer_low	66	23 (34.8)	3,166	1 (Reference)		1 (Reference)	
	D-dimer_high	67	38 (56.7)	2,405	2.07 (1.23-3.48)	0.006	1.55 (0.81-3.00)	0.188

B, D-dimer levels as continuous variables

Model	Variable	Total patients, n	Events, n (%)	Follow-up time, days	Crude HR (95% CI)	Crude P-value	Adjusted HR (95% CI)	Adjusted P-value
Model 1	D-dimer*0.1	133	61 (45.9)	5,571	1.02 (1.00-1.03)	0.017	1.01 (1.00-1.03)	0.082
Model 2	D-dimer*0.1	133	61 (45.9)	5,571	1.02 (1.00-1.03)	0.017	1.01 (1.00-1.03)	0.179
Model 3	D-dimer*0.1	133	61 (45.9)	5,571	1.02 (1.00-1.03)	0.017	1.01 (0.99-1.03)	0.485

Model 1, adjusted for age and presence of disease; model 2, adjusted for age, presence of disease, site, Lauren classification, T stage, N stage, TNM stage nerve involvement and vessel involvement. Model 3, adjusted for age, presence of disease, site, Lauren classification, T stage, N stage, TNM stage, nerve involvement, vessel involvement, postoperative chemotherapy, tissue Polypeptide Antigen, CA50, Carbohydrate Antigen 50, 199, CA724, Carbohydrate Antigen 724 and TSGF, Tumor Supplied Group of Factors.

Table IV. Table data format for inflection point analysis in Fig. 2.

Item	BK.HR	P-value
E_BK1	110.449 (106.956-113.942)	
Slope 1	0.451 (0.429-0.474)	<0.001
Slope 2	1.004 (0.997-1.011)	0.3128
Likelihood ratio test	-	0.002
Non-linear test*1	-	0.006
Non-linear test*2	-	<0.001

BK, break point; HR, hazard ratio.

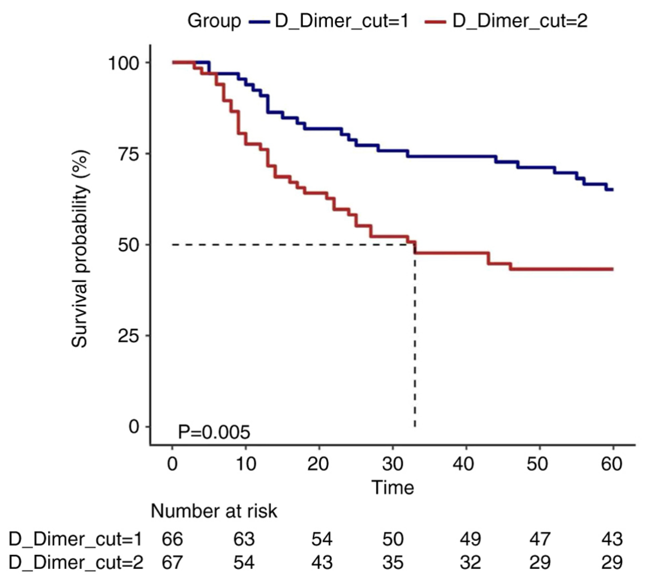

Figure 3. Kaplan-Meier survival curves of D-dimer binary classification. Cut1 and cut2 in the figure represent the D-dimer low group and D-dimer high group, respectively, after grouping based on the average value; The dashed line represents the time when the survival rate decreases to 50%.

levels from those with low D-dimer levels to a relatively high value, thus resulting in the inability to identify turning points in the curve fitting.

The current study has significant value clinically, since it could provide valuable clinical insights in the following two main areas: i) Firstly, the study demonstrated that there was a different association between the preoperative D-dimer levels and 5-year OS in different intervals. Therefore, preoperative D-dimer levels <200 ng/ml were associated with a worse prognosis, while D-dimer levels 100-200 ng/ml were associated with a better prognosis in GC. Secondly, the findings of the current study could also provide novel insights for future studies on the development of diagnostic or predictive models for assessing 5-year OS in patients with GC.

However, the present study has some limitations. Firstly, since it was necessary to record the effects of numerous covariates on D-dimer levels, a relatively small sample size was included in the study. Consequently, the sample continuity weakened after the inflection point (the rising segment on the right side of the U-shaped curve inflection point),

Table V. Multi factor regression analysis conducted by simulating the experiment by Kim and Song (27).

Variable	Total patients, n	Events, n (%)	Follow-up time, days	Crude HR (95% CI)	Crude P-value	Adjusted HR (95% CI)	Adjusted P-value
D-dimer_low	66	23 (34.8)	3,166	1 (Reference)	-	1.00 (Reference)	-
D-dimer_high	67	38 (56.7)	2,405	2.07 (1.23-3.48)	0.006	1.91 (1.13-3.22)	0.015

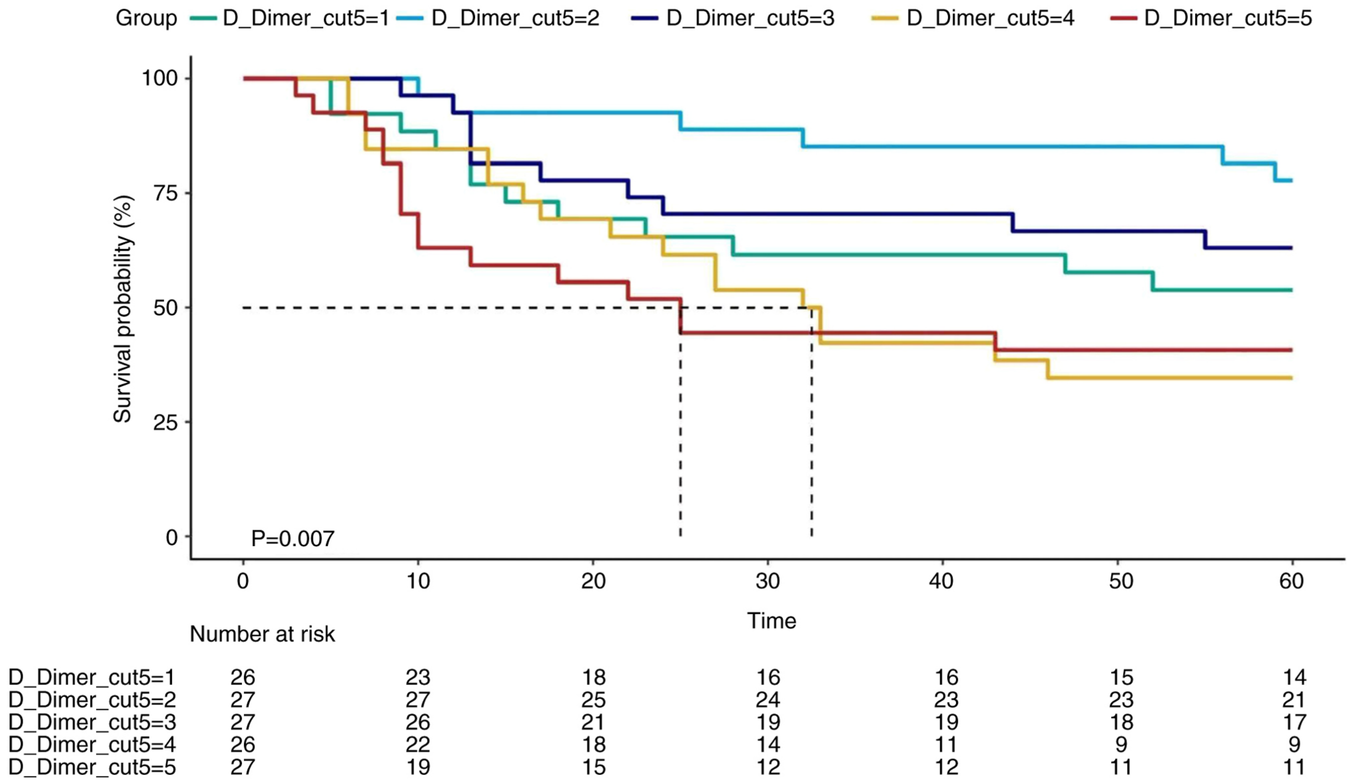

Figure 4. Kaplan-Meier survival curves of D-dimer five class classification. D_Dimer_cut5=1, D_Dimer_cut5=2, D_Dimer_cut5=3, D_Dimer_cut5=4, and D_Dimer_cut5=5 respectively represent the groups of D-dimer from low to high after being divided into five equal parts; The dashed line represents the time when the survival rate decreases to 50%.

thus resulting in insignificant P-values in the right segment of the inflection point analysis. In terms of statistics, due to the limited sample size, multivariate Cox proportional hazards models may lack sufficient statistical power. Furthermore, the exclusion of particular patients from the study could limit the generalizability of the study's findings to these individuals.

Despite its limitations, this study has also several strengths. Firstly, it focused on preoperative (on admission) D-dimer levels to avoid significant fluctuations in D-dimer values caused by different surgical types and incision size/location. Secondly, the non-linearity issue was also fully addressed and further explored. Furthermore, since the present observational study was susceptible to potential confounding factors, a strict statistical adjustment was applied to minimize residual confounders. To explore the linear and non-linear association of the independent target variable, it was evaluated as both a continuous and categorical variable. In addition, to enhance the clarity of the results, these were presented in fitting curves, inflection point analysis graphs and K-M survival curves. To the best of our knowledge, the current study is the first to reveal that there was a non-linear association between preoperative D-dimer levels and 5-year OS rate in patients with GC after surgery. Additionally, a different association between the two variables was recorded in different intervals; preoperative D-dimer levels <100 ng/ml and >200 ng/ml were associated with better and worse prognosis in GC, respectively. Finally, although only 209 cases of patients with GC were included in the study, the samples were collected from Chinese Academy of Medical Sciences Cancer Hospital Shanxi Hospital (Shanxi, China), which attracts patients from different regions of the Chinese Mainland, thus enhancing the representativeness of the results. The random selection of cases in 2017 over a 3-month period ensured the randomness of the samples. Additionally, the robust diagnosis, treatment and follow-up systems of the Chinese Academy of Medical Sciences Cancer Hospital contributed to the accuracy of the data. Overall, the results of the present study could provide novel insights into the prognosis of GC in Mainland China.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YZ, JH, RY, SW, KZ and HL contributed to the study conception and design. Material preparation, data collection and analysis were performed by HL, YZ, RY and JH. The first draft of the manuscript was written by YZ, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. HL and YZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This is a retrospective observational study that has been reviewed by the Ethics Committee of Shanxi Cancer Hospital (ethical code: KY2023138; project approval number: IIT-2023-136L). Due to the fact that this study was based on baseline data obtained from patient case data and remaining biological specimen data, and there were no adverse effects on patients, an exemption for informed consent was obtained.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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