D-dimer Can Be Used to Identify Vicious Phenotype in Gastric Cancer Patients With TNMⅡ-Ⅲ Stages: a Single Institution Experience Over 10 Years Study

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Abstract

Background

Part of gastric cancer (GC) patients in early stages still endure early relapse after systematic treatment. This study was designed to identify the value of d-dimer reflecting the bad phenotype in early GC patients.

Methods

From January 1st 2009 to January 1st 2019, 467 primary GC patients with TNM stage I-II after R₀ resection were enrolled, tumor stage was classified by the national comprehensive cancer network guideline 2019. Plasma D-dimer and associated factors were reviewed and analyzed with clinic-pathological characteristics, regularly follow up was proceed when first determined.

Results

The median follow up is 33 months, and 381/467 GC patient survived after ten years follow up. Although D-dimer was significantly elevated in old age and vascular cancer emboli positive patients. Noteworthy, D-dimer levels displayed an increase in 48/467 GC patients when the cut-off values was 1.5 mg/ml based on the ROC curve in our previous study, log-rank and Cox hazard model analysis showed D-dimer is an independent risk factor for overall survival and disease free survival in this classification.

Conclusion

Plasma D-dimer represents an easy measurement and lower cost marker for the routine testing to predict highmalignancy phenotype in stage I-II gastric cancer after R₀ resection.

Clinical registration

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1. Introduction

Gastric cancer (GC) is one of the most common malignant diseases with high mobility worldwide especially in Asia countries[1, 2]. As we know, the prognosis of patients with advanced disease is very poor, but in fact, a quarter of cancer patients in early stages based on NCCN tumor stage stratification still endure early tumor recurrence after systematic treatment[3-5]. The mechanism of this phenomenon is complicated, some researchers insist that as the heterogeneity of tumor cells, they harbored different biological characteristics which help invade into the circulation system although the primary tumor is tiny[6, 7]. So, identifying this kind of patients would potentially help to inform clinical decisions to intensify systemic, regional or local therapy in clinical practice.

D-dimer is the end product of degraded from cross-linked Fibrin, and elevated when enhanced Fibrin formation and fibrinolysis. This marker is widely used to detect patients with suspected disseminated intravascular coagulation (DIC), thromboembolic events, and myocardial infarction[8, 9]. In recent years, it has been reported that D-dimer levels increased in malignancy[10, 11]. Several studies have reported that D-dimer level is associated with tumor stage, tumor prognosis, lymph node involvement, and overall survival in patients with tumors such as lung cancer[12], breast cancer[13], esophageal cancer[14], gastric cancer[15], and colon cancer[16].

Our previous study discovered that plasma d-dimer was increased in stage IV GC patients, and patients with elevated D-dimer exhibited metastasis and subsequently got poor prognosis after a short time follow up[15, 17]. Interestingly, we noticed some patients in early TNM stages with high d-dimer levels showed poor prognosis after R0 resection and adjuvant treatment. So in this study, we focus on GC patients with TNM stage I-III after R0 resection, wondering whether plasma D-dimer could be used to identify vicious phenotype in early tumor stage of gastric cancer patients, and whether this biological marker could be a complementary factor for the prognosis of early GC patients.

2. Patients And Methods

2.1. Study design

This study was based on the hypothesis that D-dimer levels can be used to identify vicious phenotype in gastric cancer patients in early tumor stages. We firstly verified our hypothesis in ten years large-scale clinical study. Plasma D-dimer levels were assessed and reviewed more than 2000 primary GC patients and a regular follow up was proceed either, and finally 467 primary GC patients in TNM stage I-III after R0 resection following up was enrolled. Plasma D-dimer levels were compared with clinical and pathological factors. Importantly, plasma D-dimer and associated factors were analyzed with OS and PFS to estimate their value in clinical practice.

2.2. Patients

Primary cancer patients recruited in the study were diagnosed by pathological examination via endoscopic biopsy and hospitalized in the First Affiliated Hospital of Xi'an Jiaotong University, between January 1st 2009 and January 1st 2019. Patients with a history of venous thrombosis or anticoagulation therapy, cardiovascular and cerebrovascular disease, acute or chronic inflammatory disease, previous malignancy, or previous anticancer treatment were excluded. Based on the results of the clinical evaluation, 467 GC patients underwent complete resection with negative margins (R0 resection) and TNM stage I-III were pathologically diagnosed, a regular follow-up was performed for all the patients, and the follow-up for all cases was terminated in May 15th 2020. Tumor stages were recorded using the classification guidelines of NCCN[18]. Our study was approved by the Conduct of Human Ethics Committee of Xi'an Jiaotong University, and clinical registration were complete either.

2.3. Methods

In this clinical study, venous blood samples were collected in tubes with sodium citrate for the measurement of D-dimer levels, the D-dimer levels and other associated factor like fibrinogen (FIB), FDP were assayed via latex-enhanced immuneturbidimetric assay as described in our previous study[14]. Other tumor marker like plasma CEA, CA199 and CA724 levels in GC patients were assayed using the ELISA method.

2.4. Statistical analysis

Data analysis was performed using SPSS 13.0 Software (SPSS, Chicago, IL, USA). As the D-dimer levels were not normally distributed, the results of the D-dimer level tests are reported as median (M) and quartile range (25th-75th). Statistical tests were performed using the Mann-Whitney U test and the Kruskal-Wallis H test. For categorical data analysis, Chi-Square and Fisher test analysis was employed. The Kaplan-Meier method was used to estimate the distribution of survival curves, and log-rank and life tables tests were used to compare the distributions between groups. Cox proportional hazards regression analysis was performed to identify independent variables that correlated with patient survival and DFS. $P < 0.05$ was considered statistically significant.

3. Results

3.1 Patient data and D-dimer levels in stage I-II GC patients

In total, 467 GC patients (361 men and 106 women, aged 24-81 years) were included in the study. Basic patient data (age, gender and other clinical characters) and plasma D-dimer levels (median and 25th-75th percentile) are listed in Table 1. Based on the results of the clinical evaluation, all the GC patients received R₀ resection, while 111 patients with T3+ or N (+) underwent palliative chemotherapy additionally. Plasma D-dimer levels were tested and compared among different TNM stages, and the results are shown in Table 1. The results did not show significant difference of D-dimer levels among different G ($p=0.429$), TNM stages ($p=0.866$), T stages ($p=0.633$), or N stages ($p=0.506$). While the results displayed a significant increased D-dimer levels in the tumor embolus positive patients ($p=0.011$) and patients whose age over 60 years old ($p=0.012$). In addition, gender ($p=0.056$), tumor location ($p=0.149$) or if received chemotherapy ($p=0.78$) did not display a significant difference in D-dimer levels in this study. The results shown in Table 1 and Figure 1.

3.2 Identify the risk factors by overall survival analysis in stage I-II GC patients.

All the 467 patients were successfully examined during follow-up. The median follow up is 34 m (2m-95m). During the ten years follow-up, 86 of the 467 patients died; the mortality is 18.4% while the overall survival rate was 81.6%, one year survival rate is 86%, 3 years survival rate is 79%, and 5 years and 7 years survival rate is 75% and 73% by life table analysis, which were shown in Table 2

When the high and low groups were defined according to the plasma D-dimer levels at 1.5 mg/ml based on our previous study (1.5 folds than normal levels in clinical practice), 48/ 467(10.28%) GC patients

were with high D-dimer levels, the survival time was shorter in high level groups(38.21m (29.77-46.65m)) than low groups(79.85m (76.55-83.16m)), and the overall survival is 60.4% and 84.0%, respectively ($p<0.001$) from the log-rank survival analysis, shown in Figure 2. Additionally, survival time correlated with tumor invasion ($p=0.001$), TNM stages ($p=0.003$), and FIB levels ($p=0.007$) based on the log-rank survival test. However, survival time was not influenced by patient gender ($p=0.204$), age ($p=0.224$), histological grade ($p=0.231$), lymph node invasion ($p=0.530$), tumor location ($p=0.163$), vascular cancer emboli ($p=0.686$), or additional chemotherapy treatment ($p=0.685$). Moreover, survival time was not influenced by CEA levels ($p=0.542$), CA199 levels ($p=0.122$), CA724 levels ($p=0.964$) or FDP levels ($p=0.056$) by log-rank test. Shown in Table 2.

Based on the Cox proportional hazards regression analysis, survival time was influenced by D-dimer levels ($p<0.001$, Risk ratio=3.60, 95%CI: 2.13-6.08), tumor invasion ($p=0.001$, Risk ratio=1.34, 95%CI: 1.10-1.63), but FIB levels ($p=0.135$, Risk ratio=1.49, 95%CI: 0.88-2.50) did not show significant difference. The results are shown in Table 3.

3.3 Identify the risk factors with Disease-Free Survival (DFS) in stage II-III GC patients.

Tumor recurrence and Disease-Free Survival (DFS) is the most crucial clinical event associated with poor prognosis of surgical GC before death and might be regarded as more objective than mortality. In this study, 98 of the 467 patients were found tumor recurrence within the follow up, the recurrence rate was 21.0 % overall, and the 1 year recurrence is 17%, 3 years recurrence is 25%, while 5 year and 7 year recurrence is 28%, 30% respectively. Shown in Table 4.

A significant difference in DFS was observed between the GC patients with high D-dimer levels and those with low levels ($p<0.001$), and the recurrence rate is 54.17% (26/ 48) in high groups and 17.18% (72/ 419) in low groups. The result was shown in Table 4 and Figure3. Besides that, univariate analysis by log-rank test showed that tumor invasion ($p=0.002$), TNM stage($p=0.002$), Age($p=0.042$), FIB levels($p=0.003$), and FDP levels($p<0.001$) were significant predictive factors for DFS, which was not associated with lymph node invasion($p=0.530$), Gender($p=0.649$), additional treatment($p=0.377$), cancer emboli($p=0.273$), histological grade ($p=0.385$) and tumor location ($p=0.061$), CEA levels($p=0.290$), CA199 levels($p=0.203$), and CA724 levels($p=0.805$). Shown in Table 4.

However, multivariate analysis by Cox proportional hazards regression showed that only D-dimer levels ($p<0.001$, Risk ratio=5.57, 95%CI: 3.22-9.63) and tumor invasion ($p=0.002$, Risk ratio=1.34, 95%CI: 1.12-1.62) was significant independent risk factor, but FIB levels ($p=0.11$, Risk ratio=1.49, 95%CI: 0.92-2.42). FDP levels ($p=0.45$, Risk ratio=0.75, 95%CI: 0.35-1.59) and Age ($p=0.35$, Risk ratio=1.22, 95%CI: 0.81-1.85) did not show significant difference in Cox's proportional hazards model for DFS as listed in Table 5.

3.4 Effectiveness of predict OS and PFS by plasma D-dimer level based on 1.0mg/l.

In our previous study, we defined the D-dimer group by 1.5 fold, while if the levels is 1.0mg/l, the result was tested again in this study. Of the 467 patients with TNM stage II-III , 76 patients showed higher d-dimer

over the level 1.0mg/l. The survival time was short for patients with high D-dimer levels ($p < 0.001$, Risk ratio=2.70 95%CI: 1.65-4.40) based on log-rank and Cox proportional hazards regression model (Table 2 and supplement Table 1). What's more, DFS was short in patients with high D-dimer levels ($p < 0.001$, Risk ratio=3.39, 95%CI: 2.07-5.54) (Table 4 and supplement Table 2) according to both log-rank and Cox regression analyzes as well. Shown in Figure 4.

Discussion

Although in early stage, GC patients received the national comprehensive cancer network (NCCN)[18] tumor stage stratification and treatment, the heterogeneity of tumor cells and different physiological characteristics, undetectable micro-metastases in vascular might happened even in early TNM stage[5, 7]. A variety of clinical and biological variables have been proposed as prognostic molecular factors for GC, but researches on the precise molecular or factors underlying and predicting the development and progression of GC especially in early stages is rare[6, 19]. So we planed to investigate whether plasma d-dimer could be used to identify bad phenotype in GC patients with early tumor stages, and whether this factor could be used as a complementary factor for the prognosis biomarker for early GC patients.

We reviewed and followed up for ten years of GC patients with early stage. In this study, although the overall survival is favorable in early stage GC patients after R0 resection, unfortunately, patients with high d-dimer levels displayed poor outcome . In this study, plasma d-dimer did not show any significant difference by TNM stages in II-III GC patients, but it showed a significant increase in old patients over 60 years and patients with vascular cancer emboli. This result consist with our previous study on GC patients[15, 17], also in other studys[20]. However, plasma D-dimer display an high level in 48 patients with TNM stage II-III gastric cancer, when the cut-off values were determined to be 1.5 mg/ml based on the ROC curve in our previous study,`and in 76 patients by cut off value is 1.0mg/ml(normal levels is below 1.0mg/l in clinical practice). Log-rank and Cox hazard model analysis showed D-dimer is an independent risk factor for the short progress free survival (PFS) and overall survival (OS) in early GC patients with TNM II-III stages in both classification. This study firstly analyzed patients characters and progress with D-dimer level in early GC stages, and found plasma d-dimer is an independent high risk factor of worse outcome. Plasma D-dimer can be concerned to be added in clinical practice as a high risk factor like G, T, N in early tumor stages.

Why D-dimer was elevated in early stage tumors? We considered it was correlated with enhanced coagulate and fibrinolysis happened when CTCs appeared in circulation[21-23]. As fibrinogen, platelet, thrombin and other coagulation and fibrinolysis factors plays an important role in circulating tumor cell survival and metastasis[24-28], it has been suggested that the formation of platelet-fibrin-tumor cell aggregation may play a causal role in endothelial adhesion and metastatic potentia. Deposition of fibrin within adherent tumor cell-platelet aggregation can be detected as early as 5 minutes after tumor cell inoculation and persists for more than 9 hours[28]. Fibrinogen is a crucial source of bio-available fibrin to tumor cells in the vasculature, which is necessary for tumor cells survive extravasation and metastasis formation[27]. Thus, plasma D-dimer may be involved in the promotion of a pro-metastatic phenotype in

the bloodstream. While in our previous studies, plasma D-dimer levels was a useful clinical marker for hematogenous metastasis, and showed linear associate with circulation tumor cells in GC patients[17]. As a result, plasma D-dimer might be used to estimate and associated with micro-metastasis event in GC patients even in early tumor stages.

There are also some questions and limitations exist in this study. Firstly, single institution study may exist statistic bias, however, as our institution is one of large cancer center in China, the epidemic of incidence of GC is higher in location for diet or environmental reasons, so our patients are representative. Now we have proceed the multicenter clinical research on this field, and the result will be analyzed in future. Secondly is about, the number of cases and the follow up time, although we reviewed ten years cases, over 2000 GC were reviewed, only a quart of patients were in early stages, in this part of patients, 40% patients were lost to their follow up, this is the present situation of GC patients in China, tumor stages were mainly in advanced stages, and one third of patients do not proceed the regular follow up in local hospital close to their home. The third one is about the prognostic factors, we also compared and analyzed gastrointestinal tumor marker like CEA, CA724 and CA199, but no significant difference in outcomes based on this levels, maybe these tumor markers were elevated markedly in advanced tumor stages, while to FDP and FIB, although significant difference were displayed in univariate analysis by log-rank, there were mostly influenced by D-dimer in multivariate analysis, this was concise with previous study. But for histological grade, lymph node invasion, cancer emboli, which have be proved for their progress values, in this study, patients' outcome is excellent so the number of dead patients is relatively rare in TNM stageⅡ-Ⅲ, so the result may be influenced by several reasons, and more cases is need to enhance their significance.

Conclusion

This study firstly analyzed patients characters and progress with D-dimer levels in early GC stages, and found high plasma d-dimer was an independent risk factor of worse outcome, Plasma D-dimer may represent an easy method to measure and lower cost marker for the routine test to predict bad phenotype in stage Ⅱ-Ⅲ gastric cancer patients. This study not only help doctors to predict overall survival and make a distinction in early tumor stage of GC patients but also potentially help doctors inform decisions to intensify systemic, regional or local therapy in patients with high hazard when diagnosis.

Abbreviations

GC: gastric cancer, FIB: fibrinogen, FDP: fibrin degradation products, DIC: disseminated intravascular coagulation, CTC: Circulation tumor cell, CEA: carcino-embryonic antigen.

Declarations

Ethics approval and consent to participate Human Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University approved this study. All animal experiments were performed according to the

animal protection laws and were approved by the Human Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. **Consent for publication** Not applicable. **Availability of data and materials** All the data needing for conclusion and result is contained in the article

Competing Interests

There is no competing interests and all the authors have approved the submission and publication of the manuscript to this BMC Cancer.

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Author Contributions

Conceived and designed the experiments: Yao Cheng, Dongmei Diao. Chengxue Dang. Performed the experiments: Dongmei Diao, Xin Zhang, Wenxing Li, Xuan Wang, Zhe Wang, Yao Cheng, Yongchun Song. Analysed the data: Dongmei Diao, Leilei Pei. Wrote the paper: Yao Cheng, Dongmei Diao.

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Informed consent

Informed consent was obtained written from all participants

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Tables

Table 1. patients characters and Plasma D-dimer levels in Stage I-III GC patients (n=467).

Variables	No. of cases	Median	25 th -75 th percentile	<i>P</i>
Patients	467	0.50	0.20- 0.8	
Gender				0.056
Female	106	0.50	0.28- 0.96	
Male	361	0.50	0.20- 0.70	
Age				0.012*
<60	229	0.40	0.20- 0.70	
≥60	238	0.50	0.20- 0.93	
Histological grade				0.429
G1	48	0.35	0.13- 0.70	
G2	195	0.50	0.20- 0.85	
G3+G4	200	0.50	0.20- 0.80	
Gx	24	0.45	0.20- 0.68	
Tumor invasion				0.633
T0	6	0.250	0.00- 0.63	
T1	216	0.50	0.20- 0.80	
T2	107	0.50	0.20- 0.75	
T3	102	0.50	0.20- 1.00	
T4	36	0.50	0.30- 0.70	
Lymph node invasion				0.506
N0	403	0.50	0.20- 0.80	
N1	51	0.40	0.20- 0.80	
N2	13	0.50	0.10- 0.60	
TNM Stage				0.866
Tis	5	0.30	0.10- 0.75	
IA	192	0.50	0.20- 0.80	
IB	93	0.50	0.20- 0.80	
IIA	120	0.45	0.20- 0.88	
IIB	57	0.50	0.20- 0.70	

Cancer embolus				0.011*
Negative	443	0.50	0.20- 0.80	
Positive	24	0.70	0.40- 1.34	
Location				0.149
Cardia	114	0.50	0.20- 0.81	
Corpus	94	0.50	0.20- 0.80	
Pylorus	178	0.40	0.10- 0.70	
x	81	0.50	0.30- 0.90	
Chemo-therapy				0.780
No	356	0.50	0.20- 0.80	
Yes	111	0.50	0.20- 0.80	

Footnote: P value was analyzed via the Mann-Whitney U test and the Kruskal-Wallis H test; * indicates p-value ≤ 0.05 (2-tailed).

Table 2. log-rank and life table analysis of prognosis factors for OS in Stage I-III GC patients (n=467).

Variables	No. of cases	OSR	1-OSR	3-OSR	5-OSR	7-OSR	Mean	95%CI	P
Patients	86/ 467	81.6%	86%	79%	75%	73%	77.46	74.14-80.79	
Gender									0.204
Female	16/ 106	84.9%	90%	81%	81%	81%	77.17	71.42-82.93	
Male	70/ 361	80.6%	84%	79%	74%	70%	76.28	72.36-80.19	
Age									0.224
<60	38/ 229	83.4%	88%	81%	77%	77%	79.25	74.71-83.79	
≥60	48/ 238	79.8%	84%	77%	74%	-	66.31	62.40-70.23	
Histological grade									0.231
G1	5/ 48	89.6%	93%	86%	86%	86%	85.58	77.83-93.32	
G2	40/ 195	79.5%	82%	78%	73%	73%	75.52	70.46-80.59	
G3+G4	37/ 200	81.5%	87%	77%	74%	68%	75.13	69.67-80.59	
Tumor invasion									0.001**
T0+T1	28/ 222	87.4%	90%	85%	83%	83%	83.35	79.32-87.39	
T2	20/ 107	81.3%	86%	79%	72%	63%	74.97	67.64-82.29	
T3	30/ 102	70.6%	70%	67%	67%	67%	59.32	51.54-66.10	
T4	8/ 36	77.8%	97%	76%	54%	54%	59.89	50.04-69.74	
Lymph node invasion									0.530
N0	72/ 403	82.1%	86%	79%	77%	74%	78.0	74.47-81.54	
N1	10/ 51	80.4%	86%	81%	72%	72%	69.82	61.45-78.19	
N2+N3	4/ 13	69.2%	83%	65%	-	-	46.57	37.51-	

								55.63	
TNM Stage									0.003**
Tis +IA	25/ 197	87.3%	90%	85%	83%	83%	83.47	79.26-87.68	
IB	14/ 93	84.9%	86%	83%	83%	69%	78.83	71.43-86.23	
IIA	32/ 120	73.3%	76%	71%	66%	66%	63.75	57.48-70.02	
IIB	15/ 57	73.7%	89%	70%	57%	57%	60.14	51.06-69.22	
Cancer embolus									0.686
Negative	81/ 443	81.7%	86%	79%	75%	73%	77.56	74.15-80.97	
Positive	5/ 24	79.2%	82%	76%	76%	-	66.62	53.98-79.26	
Location									0.163
1	23/ 114	79.8%	81%	75%	75%	75%	67.93	61.76-74.10	
2	15/ 94	84.0%	92%	86%	76%	67%	78.96	72.19-85.73	
3	27/ 178	84.8%	90%	83%	81%	81%	81.74	77.17-86.31	
Chemo-therapy									0.685
No	63/ 356	82.3%	84%	79%	78%	75%	78.43	74.73-82.13	
Yes	23/ 111	79.3%	89%	79%	67%	67%	68.35	62.47-74.30	
D-dimer									<0.001**
<1.5mg/l	67/ 419	84.0%	88%	82%	78%	76%	79.85	76.55-83.16	
≥1.5mg/l	19/ 48	60.4%	63%	46%	46%	-	38.21	29.77-46.65	
D-dimer									<0.001**
<1.0mg/l	62/ 329	84.1%	88%	83%	79%	76%	80.14	76.76-83.51	
≥1.0mg/l	24/ 76	68.4%	70%	56%	56%	-	49.74	41.49-58.00	

FDP									0.056
≤5mg/l	79/ 443	82.2%	86%	80%	76%	73%	78.05	74.69-81.41	
>5mg/l	7/ 24	70.8%	74%	67%	67%	-	48.05	36.87-59.24	
FIB									0.007**
≤4mg/l	66/ 394	83.2%	87%	81%	78%	75%	79.31	75.87-82.75	
>4mg/l	20/ 73	72.6%	76%	65%	60%	-	57.73	49.37-66.09	
CEA									0.542
≤3.4 ng/ml	32/ 247	87.0%	89%	86%	84%	77%	82.37	78.16-86.58	
> 3.4 ng/ml	10/ 63	84.1%	88%	80%	80%	80%	68.72	61.81-75.63	
CA724									0.964
≤6.9 U/ml	27/ 241	88.8%	92%	88%	86%	79%	84.31	80.41-88.22	
>6.9 U/ml	3/ 30	90.0%	96%	84%	84%	-	65.28	58.21-72.36	
CA199									0.122
≤39 U/ml	27/ 259	89.6%	93%	88%	87%	81%	85.01	81.35-88.68	
>39 U/ml	3/ 14	78.6%	84%	65%	65%	-	56.43	41.42-71.45	

Footnote: * Indicates that the correlation was significant at the 0.05 level (2-tailed). ** Indicates that the correlation was significant at the 0.01 level (2-tailed). CI, confidence interval.

Table 3 Log-rank and Cox proportional hazards regression model of Prognostic variables for OS in GC patients (n=467).

Variable	<i>P</i> (uni)	<i>P</i> (multi)	RR (95% CI)
D-dimer	<0.001**	<0.001**	3.60 (2.13, 6.08)
T	0.001*	0.004**	1.34 [1.10, 1.63]
FIB	0.007	0.14	1.49 (0.88- 2.50)

Footnote: * Indicates that the correlation was significant at the 0.05 level (2-tailed). ** Indicates that the correlation was significant at the 0.01 level (2-tailed). RR, Risk Ratio; CI, confidence interval.

Table 4. log-rank and life table analysis of prognosis factors for DFS in Stage I-II GC patients (n=467).

Variables	No. of cases	PFSR	1-PFSR	3-OSR	5-OSR	7-OSR	Median	95%CI	P
Patients	98/ 467	79.0%	83%	75%	72%	70%	77.46	74.14-80.79	
Gender									0.649
Female	22/ 106	79.2%	86%	75%	73%	73%	72.60	66.23-78.97	
Male	76/ 361	78.9%	82%	75%	72%	69%	74.78	70.77-78.79	
Age									0.042*
<60	40/ 229	82.5%	86%	80%	77%	77%	78.59	74.01-83.17	
≥60	58/ 238	75.6%	80%	71%	68%	-	63.03	58.86-67.20	
Histological grade									0.385
G1	7/ 48	85.4%	93%	79%	79%	79%	81.05	71.72-90.38	
G2	44/ 195	77.4%	79%	77%	71%	71%	73.85	68.64-79.05	
G3+G4	42/ 200	79.0%	84%	72%	72%	66%	74.88	67.39-78.57	
Tumor invasion									0.001**
T0+T1	33/ 222	85.1%	89%	82%	79%	79%	81.14	76.79-85.48	
T2	23/ 107	78.5%	81%	77%	70%	61%	72.69	65.15-80.23	
T3	32/ 102	68.6%	69%	66%	66%	66%	57.82	50.89-64.76	
T4	10/ 36	72.2%	91%	55%	55%	-	56.98	46.90-67.07	
Lymph node invasion									0.530
N0	81/ 403	79.9%	83%	75%	74%	71%	75.92	72.24-79.60	
N1	13/ 51	74.5%	79%	77%	65%	65%	69.82	56.24-74.47	

N2+N3	4/ 13	69.2%	83%	65%	-	-	46.57	34.26-54.55
TNM Stage								0.002**
Tis +IA	28/ 197	85.8%	89%	83%	81%	81%	81.92	77.46-86.38
IB	18/ 93	80.6%	83%	78%	75%	62%	74.11	65.91-82.30
IIA	35/ 120	70.8%	72%	69%	64%	64%	62.13	55.77-68.50
IIB	17/ 57	70.2%	83%	57%	57%	-	58.47	49.54-67.40
Cancer embolus								0.273
Negative	91/ 443	79.5%	83%	76%	73%	70%	75.56	72.03-79.09
Positive	7/ 24	70.8%	77%	68%	57%	-	59.21	44.96-73.46
Location								0.061
1	28/ 114	75.4%	77%	69%	69%	69%	64.39	57.86-70.93
2	16/ 94	83.0%	90%	82%	75%	66%	78.96	70.73-84.77
3	31/ 178	82.6%	89%	80%	78%	78%	81.74	74.85-84.54
Chemo-therapy								0.377
No	70/ 356	80.3%	82%	77%	76%	72%	76.49	72.61-80.36
Yes	28/ 111	74.8%	84%	71%	62%	62%	65.09	58.92-71.25
D-dimer								<0.001**
<1.5mg/l	72/ 419	82.8%	87%	80%	77%	74%	78.81	75.43-82.19
≥1.5mg/l	26/ 48	45.8%	47%	24%	24%	-	30.49	23.05-37.93
D-dimer								<0.001**
≤1.0mg/l	66/ 391	83.1%	87%	81%	78%	75%	79.33	75.90-82.76

>1.0mg/l	32/ 76	57.9%	58%	41%	36%	-	41.56	33.47-49.65
FDP	<0.001**							
≤5mg/l	87/ 443	80.4%	84%	77%	74%	71%	76.39	72.91-79.86
>5mg/l	11/ 24	54.2%	61%	42%	42%	-	38.86	27.75-49.98
FIB	0.003**							
≤4mg/l	75/ 319	81.0%	85%	78%	75%	72%	77.12	73.51-80.73
>4mg/l	23/ 73	68.5%	70%	58%	58%	-	54.87	46.34-63.40
CEA	0.290							
≤3.4	37/ 247	85.0%	86%	83%	82%	75%	80.41	75.97-84.84
> 3.4	13/ 63	79.4%	88%	74%	70%	-	64.84	57.25-72.43
CA724	0.805							
≤6.9	31/ 241	87.1%	90%	86%	84%	77%	82.511	78.33-86.68
>6.9	4/ 30	86.7%	96%	76%	76%	-	63.41	55.80-71.03
CA199	0.203							
≤39	27/ 259	87.6%	91%	86%	84%	78%	82.96	79.00-86.93
>39	3/ 14	78.6%	84%	72%	72%	-	55.93	40.39-71.48

Footnote: * indicates p-value ≥ 0.05 (2-tailed). R indicates the correlation coefficient. ** indicates p-value ≥ 0.01 (2-tailed).

Table 5 Log-rank and Cox proportional hazards regression model of Prognostic variables for DFS in GC patients (n=467).

Variable	<i>P</i> (uni)	<i>P</i> (multi)	RR (95% CI)
D-dimer	<0.001**	<0.001**	5.57 (3.22, 9.63)
T	0.001*	0.002**	1.34 (1.12, 1.62)
FIB	0.003**	0.11	1.49 (0.92- 2.42)
FDP	0.002**	0.45	0.75 (0.35- 1.59)
AGE	0.042*	0.35	1.22(0.81- 1.85)

Footnote: * Indicates that the correlation was significant at the 0.05 level (2-tailed). ** Indicates that the correlation was significant at the 0.01 level (2-tailed). RR, Risk Ratio; CI, confidence interval.

Figures

Figure 1

Plasma D-dimer levels in GC patients with stage $\geq$ II. dimer levels were significantly higher in old age patients over 60 years old ($p=0.012$)(A) and cancer embolus positive($p=0.011$) (B) ; But D-dimer levels did not display any differences in different tumor invasion ($p=0.633$) (C) , lymph node invasion ($p=0.506$) (D) , and TNM stage ($p=0.866$) (E).

Figure 2

Kaplan-Meier analysis of overall survival in GC patients with stage II-III. A, The survival rate was lower in patients with D-dimer levels over 1.5 mg/l; B. the survival rate was decreased with tumor invasion.

Figure 3

Kaplan-Meier analysis of disease free survival in GC patients with stage II-III. A. The DFS rate was lower in patients with D-dimer levels over 1.5 mg/l; B. The DFS rate was decreased with tumor invasion as well.

Figure 4

Kaplan-Meier analysis of OS and DFS in GC patients with stage II-III. A. The DFS rate was lower in patients with D-dimer levels over 1.0 mg/l; B. The DFS rate was decreased with D-dimer levels over 1.0 mg/l as well.

Supplementary Files

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- [renamedccf73.pdf](#)
- [SupplementTable12.docx](#)