Combined preoperative plasma fibrinogen and D-Dimer concentration as a prognostic marker of endometrial cancer

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Abstract

Endometrial cancer (EC) is one of the most common gynecological malignancies. The aim of this study was to evaluate the combined prognostic value of D-dimer and fibrinogen in EC patients. We evaluated the prognostic value of preoperative plasma fibrinogen and D-Dimer concentration in EC patients using Kaplan-Meier curve analysis and Cox proportional hazards regression model. Kaplan-Meier curve analysis demonstrated that EC patients with higher levels of plasma fibrinogen or D-Dimer had a significantly poorer overall survival (OS) and recurrence-free survival (RFS). Furthermore, combination of fibrinogen and D-Dimer levels significantly improved the efficacy for predicting RFS of EC patient. Patients with higher fibrinogen or D-Dimer levels exhibited a significantly poorer RFS in both the univariate and multivariate analysis. In conclusions, the preoperative plasma fibrinogen and D-Dimer concentrations may serve as potential prognostic factors for EC patients, and combination of fibrinogen and D-Dimer concentration may be a potential marker for predicting RFS of EC patients.

Introduction

Endometrial cancer (EC) is one of the most common gynecological malignancies with a rising incidence and mortality [11, 19]. In recent years, the incidence and mortality rates of EC have increased in developing countries, which accounts for nearly 7% of new cancer cases and more than 2% of deaths, especially in China [32]. Most EC patients are diagnosed post menopause and surgery is the primary treatment [10]. Despite successful surgery, 10–15% of patients develop recurrence or metastasis within 5 years, for whom a few treatment options are available and a poor prognosis is associated [4]. Therefore, it is necessary to identify the novel prognostic biomarkers for predicting clinical outcomes of EC patients undergoing surgical treatment.

Accumulating evidence has demonstrated that the hemostatic system is implicated in cancer development, growth, and metastasis [9]. Abnormal activation of the coagulation/fibrinolytic system, especially plasma dimerized plasmin fragment D (D-dimer) and fibrinogen, has been frequently identified in cancer patients [2, 30]. D-dimer is a final degradation product of crossed-link fibrin and a marker for activation of coagulation/fibrinolytic system [17]. Elevated D-dimer levels have been detected in patients with lung [1, 17], prostate [25], colorectal carcinoma [3, 15] and EC [24]. Fibrinogen is a bridging molecule, which is commonly involved in the process of hemostasis and is a key protein in the coagulation pathway and clot formation [6]. The important role of fibrinogen in carcinogenesis has been demonstrated in some tumor types, which is identified as a major component of tumor stroma [26]. The prognostic values of D-dimer and fibrinogen have been investigated in various cancer types [17, 20, 23, 35]. Several researches detected the combined effect of D-dimer and fibrinogen on prognosis of cancer, including epithelial ovarian cancer [22], pancreatic carcinoma [5], small cell lung cancer [36], renal cell carcinoma [8] and colorectal carcinoma [33]. However, the combined prognostic value of D-dimer and fibrinogen in EC patients remains unknown.

In this study, we investigated the ability of preoperative plasma D-dimer and fibrinogen concentration to predict prognosis of EC patients. Further, we evaluated the combined effects of D-dimer and fibrinogen on prognosis of EC patients.

Materials And Methods

Patients

A total of 337 patients who underwent EC surgery were enrolled between March 2012 and November 2017, at the Nanyang central Hospital. All patients were newly diagnosed with EC by dynamic imaging (CT/MRI scans) and confirmed by histology. The concentrations of fibrinogen and D-Dimer in EC patients' plasma were measured one week before surgery for further analysis. Detailed clinical information including age, FIGO stage, histological grade, lymph node metastasis, depth of myometrial invasion, and menopausal status were collected by physicians through medical chart review. The follow-up was performed by trained clinical specialist and the latest follow-up data were obtained in November, 2017. This study was approved by Ethics Committee of Henan University.

Statistical Analysis

Statistical analyses were performed by SPSS version 20.0 software package (IBM, Armonk, NY, USA). Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. Log-rank test was used to analyze the difference between groups. Kaplan-Meier curve analysis was used to calculate cumulative survival time in patients. A $P < 0.05$ in two-sided tests was considered statistically significant in this study.

Results

Characteristics of the study population

A total 337 EC patients were analyzed in this study and clinical characteristics of all patients were summarized in Table 1. The median age of all patients at the time of EC diagnosis was 52 years. Histological stratification of EC patients was determined using the World Health Organization Histological Grading System [28] and most patients were histological grade G1-G2 (N = 253, 75%). Majority of patients were early FIGO stage Ⅰ-Ⅱ (N = 299, 88.7%), according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system [27]. There were 8.3% (N = 28) of patients who had depth of myometrial invasion > 1/2, and 5.9% (N = 20) of patients who had lymph node metastasis. Moreover, there were 187 (55.5%) patients in post-menopausal status. During the follow-up, 15 (4.5%) patients died, and 30 (8.9%) patients showed symptoms of recurrence (Table 1).

Table 1
The characteristics of study population

Variables	Number (n = 337, %)
Age (years), mean ± SD	52 ± 9.686
Histological grade	
G1-G2	253(75.0)
G3	43 (12.8)
Unknown	41(12.2)
FIGO stage	
I-II	299(88.7)
III-IV	38(11.3)
Depth of myometrial invasion	
≤ 1/2	309(91.7)
> 1/2	28(8.3)
Lymph node metastasis	
No	317(94.1)
Yes	20(5.9)
Menopause	
No	150(44.5)
Yes	187(55.5)
Death	
No	322(95.5)
Yes	15(4.5)
Recurrence	
No	307(91.1)
Yes	30(8.9)

Association between clinical characteristics and prognosis of EC patients

The prognostic significance of clinical characteristics on EC patients was assessed using univariate and multivariate analyses by Cox proportional hazards regression model. Univariate analysis indicated that there was a significantly poor prognosis in older patients, in the patients with late histological (G3) and FIGO stage (III-IV), and in the patients with depth of myometrial invasion (Table 2). Furthermore, the patients with lymph node metastasis had a poorer recurrence-free survival (RFS) and postmenopausal patients had a poorer overall

survival (OS) (Table 2). As shown in Table 3, the multivariate analysis demonstrated that late FIGO stage (III-IV) (HR 6.86, 95% CI: 1.63–28.80, $P = 0.009$) and depth of myometrial invasion > 1/2 stage (HR 6.24, 95% CI: 1.57–24.73, $P = 0.009$) were significantly associated with poor OS of EC patients. Moreover, the FIGO stage was also remarkably associated with RFS (HR 7.07, 95% CI: 2.44–20.47, $P = 3.1\times10^{-4}$). In brief, the poor clinical outcomes were observed in EC patients with late FIGO stage (III-IV) (Table 3).

Table 2
Association between characteristics and prognosis of EC patients by univariate analyses

Characteristic	Overall survival				Recurrence-free survival			
	Alive	Dead	HR(95% CI)	*P* value	No	Yes	HR(95% CI)	*P* value
Age								
≤ 52	166	3	1		160	9	1	
> 52	156	12	4.05(1.14–14.45)	**0.031**	147	21	2.35(1.07–5.14)	**0.033**
Histological grade								
G1-G2	246	7	1		239	14	1	
G3	39	4	5.25(1.51–18.23)	**0.009**	36	7	4.14(1.66–10.34)	**0.002**
Unknown	37	4			32	9		
FIGO stage								
I-II	289	10	1		279	20	1	
III-IV	33	5	5.20(1.74–15.55)	**0.003**	28	10	5.07(2.35–10.97)	**3.6×10^{-5}**
Depth of myometrial invasion								
≤ 1/2	299	10	1		285	24	1	
> 1/2	23	5	8.47(2.81–25.51)	**1.5×10^{-4}**	22	6	4.09(1.65–10.12)	**0.002**
Lymph node metastasis								
No	304	13	1		292	25	1	
Yes	18	2	2.82(0.63–12.64)	0.177	15	5	3.27(1.24–8.64)	**0.017**
Menopause								
No	149	1	1		143	7	1	
Yes	173	14	10.01(1.31–76.30)	**0.026**	164	23	2.32(0.99–5.42)	0.052

CI, Confidence interval; HR, hazard ratio.

Table 3
Association between clinical characteristics and prognosis of EC patients by multivariate analyses.

Characteristic	Overall survival				Recurrence-free survival			
	Alive	Dead	HR*(95% CI)	*P* value	No	Yes	HR*(95% CI)	*P* value
Age								
≤ 52	166	3	1		160	9	1	
> 52	156	12	1.26(0.24–6.51)	0.782	147	21	1.72(0.54–5.46)	0.358
Histological grade								
G1-G2	246	7	1		239	14	1	
G3	39	4	1.77(0.46–6.77)	0.403	36	7	2.15(0.79–5.89)	0.135
Unknown	37	4			32	9		
FIGO stage								
I-II	289	10	1		279	20	1	
III-IV	33	5	6.86(1.63–28.80)	**0.009**	28	10	7.07(2.44–20.47)	**3.1×10^{-4}**
Depth of myometrial invasion								
≤ 1/2	299	10	1		285	24	1	
> 1/2	23	5	6.24(1.57–24.73)	**0.009**	22	6	2.89(0.97–8.59)	0.057
Lymph node metastasis								
No	304	13	1		292	25	1	
Yes	18	2	0.19(0.03–1.46)	0.111	15	5	0.35(0.09–1.35)	0.128
Menopause								
No	149	1	1		143	7	1	
Yes	173	14	4.33(0.39–47.77)	0.231	164	23	0.90(0.26–3.11)	0.866

HR*: adjusted by Age, Histological grade, FIGO stage, Depth of myometrial invasion, Lymph node metastasis, Menopause;

CI, Confidence interval; HR, hazard ratio.

Prognostic analysis of preoperative plasma fibrinogen and D-Dimer concentration in EC patient

The association between preoperative plasma fibrinogen concentration and prognosis of EC patients was investigated. The patients were first divided into two subgroups by the ROC cut-off value (2.84 g/L), median (2.69 g/L) and clinical value (4.00 g/L) of fibrinogen. The prognostic significance of preoperative plasma fibrinogen levels on OS and RFS of EC patients was estimated by Cox regression model using univariate and multivariate analyses. As the data shown in Table 4, univariate analysis indicated that higher plasma fibrinogen was significantly associated with poorer OS in EC patients (HR 4.96, 95% CI: 1.58–15.63, *P* = 0.006 by ROC cut-off value; HR 4.96, 95% CI: 1.40-17.59, *P* = 0.013 by median; HR 5.82, 95% CI: 1.61–20.98, *P* = 0.007 by clinical value). Multivariate analysis revealed that higher plasma fibrinogen remained to be significantly associated with poorer OS in EC patients when divided by the ROC cut-off value (HR 3.84, 95% CI: 1.14–12.94, *P* = 0.030) and clinical value (HR 3.90, 95% CI: 1.01-15.00, *P* = 0.048). However, there was no significant association between OS of EC patients and preoperative plasma fibrinogen levels when divided by the median using multivariate analysis. The similar results were observed in RFS of EC patients. The higher plasma fibrinogen was significantly associated with poorer RFS in EC patients using univariate analysis. However, multivariate analyses revealed that higher preoperative plasma fibrinogen levels remained to be significantly associated with poorer RFS in EC patients only when divided patients by ROC cut-off value (HR 3.73, 95% CI: 1.60–8.72, *P* = 0.002). Therefore, we performed further analyses by ROC cut-off value of preoperative plasma

fibrinogen levels. Kaplan-Meier curve analysis demonstrated that EC patients with higher plasma fibrinogen levels had a significantly poorer OS ($P = 0.002$) and RFS ($P = 3.1 \times 10^{-5}$) (Fig. 1(, ,B)).

Table 4
The prognosis analyses for FIB and D-dimer in EC patients

values	Overall survival					Recurrence-free survival				
	Alive/Dead	HR(95% CI)	*P* value	HR*(95% CI)	*P* value	No/Yes	HR(95% CI)	*P* value	HR*(95% CI)	*P* value
FIB values										
By ROC cut-off value										
≤ 2.84 g/L	191/4	1		1		187/8	1		1	
> 2.84 g/L	131/11	4.96(1.58–15.63)	**0.006**	3.84(1.14–12.94)	**0.030**	120/22	4.76(2.12–10.72)	**1.63×10^{-4}**	3.73(1.60–8.72)	**0.002**
By median										
≤median (2.69 g/L)	166/3	1		1		162/7	1		1	
>median (2.69 g/L)	156/12	4.96(1.40-17.59)	**0.013**	2.25(0.57–8.91)	0.247	145/23	3.90(1.67–9.10)	**0.002**	2.51(1.00-6.28)	0.049
By clinical value										
≤ 4 g/L	304/12	1		1		290/26	1		1	
> 4 g/L	18/3	5.82(1.61–20.98)	**0.007**	3.90(1.01-15.00)	**0.048**	17/4	3.46(1.20-10.01)	**0.022**	1.91(0.62–5.89)	0.261
D-dimer values										
By ROC cut-off value										
≤ 0.16 mg/L	228/3	1		1		213/12	1		1	
> 0.16 mg/L	94/12	7.62(2.14–27.17)	**0.002**	6.20(1.67–22.99)	**0.006**	94/18	2.49(1.19–5.19)	**0.015**	2.14(1.00-4.58)	**0.050**
By median										
≤median (0.11 mg/L)	168/1	1		1		160/9	1		1	
>median (0.11 mg/L)	154/14	14.70(1.88-114.75)	**0.01**	13.69(1.67-112.23)	**0.015**	147/21	2.01(0.91–4.34)	0.085	1.75(0.77–3.99)	0.182
By clinical value										
≤ 0.5 mg/L	168/1	1		1		291/24	1		1	
> 0.5 mg/L	154/14	5.01(1.57–16.01)	**0.007**	2.10(0.52–8.45)	0.295	16/6	3.57(1.44–8.82)	**0.006**	1.63(0.58–4.54)	0.352

values	Overall survival					Recurrence-free survival				
	Alive/Dead	HR(95% CI)	*P* value	HR*(95% CI)	*P* value	No/Yes	HR(95% CI)	*P* value	HR*(95% CI)	*P* value
HR*: adjusted by Age, Histological grade, FIGO stage, Depth of myometrial invasion, Lymph node metastasis, Menopause;										
FIB, fibrinogen; CI, Confidence interval; HR, hazard ratio.										

To assess the prognostic significance of preoperative plasma D-Dimer concentration in EC patient, we first divided the patients into two subgroups by the ROC cut-off value (0.16 mg/L), median (0.11 mg/L) and clinical value (0.5 mg/L) of D-Dimer. As shown in Table 4, patients with higher preoperative plasma D-Dimer concentration had significantly poorer OS (HR 7.62, 95% CI: 2.14–27.17, $P = 0.002$ by univariate analyses; HR 6.20, 95% CI: 1.67–22.99, $P = 0.006$ by multivariate analyses) and RFS (HR 2.49, 95% CI: 1.19–5.19, $P = 0.015$ by univariate analyses; HR 2.14, 95% CI: 1.00-4.58, $P = 0.050$ by multivariate analyses) when divided patients by ROC cut-off value. The higher preoperative plasma D-Dimer concentration was significantly associated with poorer OS in EC patients using both univariate and multivariate analyses when divided patients by median value. However, there was no statistical association in plasma D-Dimer concentration and RFS in EC patients when divided patients by median value. Furthermore, only positive relation was observed using univariate analyses when divided patients by clinical value (Table 4). We performed further analyses by ROC cut-off value of preoperative plasma D-Dimer levels. Moreover, Kaplan-Meier curve analysis showed that EC patients with higher plasma D-Dimer levels had a significantly poorer OS ($P = 2.31 \times 10^{-4}$) and RFS ($P = 0.022$) (Fig. 1(, ,D)).

Prognostic analysis of preoperative plasma fibrinogen and D-Dimer concentration in EC patients stratified by host characteristics

As shown in Table 4, some clinical characteristics were significantly associated with OS of EC patients by univariate analysis. These clinical characteristics may be confounding factors for the prognostic value of preoperative plasma fibrinogen and/or D-Dimer concentration on OS and RFS of EC patients. Therefore, we further investigated the effects of preoperative fibrinogen and D-Dimer concentration on the OS and RFS of EC patients stratified by host characteristics using multivariate analyses. As shown in Table 5, the higher preoperative plasma fibrinogen levels in patients without depth of myometrial invasion exhibited a significantly poorer OS (HR 5.82, 95% CI 1.11–30.64, $P = 0.038$) and RFS (HR 4.31, 95% CI 1.63–11.43, $P = 0.003$). Higher preoperative plasma fibrinogen levels were also prognostic factors for poorer RFS in older patients, and in the patients without lymph node metastasis and in post-menopausal status. Meanwhile, the higher preoperative plasma D-Dimer levels in patients without lymph node metastasis exhibited a significantly poorer OS (HR 5.03, 95% CI 1.32–19.22, $P = 0.018$) and RFS (HR 2.32, 95% CI 1.01–5.30, $P = 0.047$) (Table 6). In addition, higher preoperative plasma D-Dimer levels were also prognostic factors for poorer OS in older patients, in the patients with lower FIGO (I-II) stage, and in the patients without lymph node metastasis and in post-menopausal status (Table 6).

Table 5
The association between FIB and prognosis of EC patients stratified by host characteristics.

FIB	Overall survival			Recurrence-free survival		
	Total/Dead	HR*(95% CI)	*P* value	Total/Recurrence	HR*(95% CI)	*P* value
Age						
Younger (≤ 53)						
≤ 2.84	112/1	1		112/3	1	
> 2.84	57/2	1.66(0.06–46.74)	0.765	57/6	3.09 (0.68–13.95)	0.143
Older(>53)						
≤ 2.84	83/3	1		83/5	1	
> 2.84	85/9	3.15(0.78–12.74)	0.107	85/16	**3.78 (1.29–11.06)**	**0.015**
Histological grade						
G1-G2						
≤ 2.84	157/2	1		152/5	1	
> 2.84	96/5	3.74(0.66–21.35)	0.138	87/9	2.91 (0.94–9.01)	0.064
G3						
≤ 2.84	17/2	1		15/2	1	
> 2.84	26/2	0.75(0.05–12.17)	0.839	21/5	0.75 (0.06–8.86)	0.818
Unknown						
≤ 2.84	21/0			21/1		
> 2.84	20/4	NA		10/8	NA	
FIGO stage						
I-II						
≤ 2.84	176/3	1		176/7	1	
> 2.84	123/7	2.51(0.59–10.70)	0.214	123/13	2.55 (0.98–6.62)	0.054
III-IV						
≤ 2.84	19/1	1		19/1	1	
> 2.84	19/4	62.37(0.001-4.1×10^6)	0.465	19/9	11.64 (0.44-311.29)	0.143
Depth of myometrial invasion						
≤ 1/2						
≤ 2.84	184/2	1		184/6	1	
> 2.84	125/8	5.82(1.11–30.64)	**0.038**	125/18	4.31 (1.63–11.43)	**0.003**
> 1/2						
≤ 2.84	11/2	1		11/2	1	
> 2.84	17/3	1.61(0.16–16.28)	0.685	17/4	1.84 (0.18–18.91)	0.609

HR*: adjusted by Age, Histological grade, FIGO stage, Depth of myometrial invasion, Lymph node metastasis, Menopause; FIB, fibrinogen;

CI, Confidence interval; HR, hazard ratio; NA, Not suitable for analysis.

FIB	Overall survival			Recurrence-free survival		
	Total/Dead	HR*(95% CI)	*P* value	Total/Recurrence	HR*(95% CI)	*P* value
Lymph node metastasis						
No						
≤ 2.84	185/3	1		185/7	1	
> 2.84	132/10	3.55(0.91–13.94)	0.069	132/18	**3.58 (1.43–8.95)**	**0.006**
Yes						
≤ 2.84	10/1	1		10/1		
> 2.84	10/1	1.00(0-9.6×10^{14})	1.000	10/4	NA	
Menopause						
No						
≤ 2.84	95/0	1		95/2	1	
> 2.84	55/1	1.00(0.01–82.96)	1.000	55/5	4.53 (0.84–24.51)	0.079
Yes						
≤ 2.84	100/4	1		100/6	1	
> 2.84	87/10	2.82(0.81–9.85)	0.104	87/17	3.35 (1.23–9.10)	0.018

HR*: adjusted by Age, Histological grade, FIGO stage, Depth of myometrial invasion, Lymph node metastasis, Menopause; FIB, fibrinogen;

CI, Confidence interval; HR, hazard ratio; NA, Not suitable for analysis.

Table 6
The association between D-dimer and prognosis of EC patients stratified by host characteristics

D-dimer	Overall survival			Recurrence-free survival		
	Total/Dead	HR*(95% CI)	*P* value	Total/Recurrence	HR*(95% CI)	*P* value
Age						
Younger (≤ 53)						
≤ 0.16	124/0			121/3	1	
> 0.16	45/3	NA		48/6	2.63 (0.54–12.90)	0.235
Older (> 53)						
≤ 0.16	107/3	1		104/9	1	
> 0.16	61/9	4.09(1.06–15.86)	**0.041**	64/12	1.73 (0.69–4.33)	0.239
Histological grade						
G1-G2						
≤ 0.16	177/3	1		165/7	1	
> 0.16	76/4	2.55(0.55–11.92)	0.233	74/7	1.49 (0.52–4.29)	0.457
G3						
≤ 0.16	30/0			26/3	1	
> 0.16	13/4	NA		10/4	1.28 (0.17–9.54)	0.808
Unknown						
	20/0			24/2		
	17/4	NA		17/7	NA	
FIGO stage						
I-II						
≤ 0.16	209/3	1		204/9	1	
> 0.16	90/7	4.46(1.11–17.94)	**0.035**	95/11	2.03 (0.82–5.01)	0.126
III-IV						
≤ 0.16	22/0			21/3	1	
> 0.16	16/5	NA		17/7	1.25 (0.23–6.87)	0.801
Depth of myometrial invasion						
≤ 1/2						
≤ 0.16	218/1	1		213/11	1	
> 0.16	91/9	16.05(1.87–137.50)	**0.011**	96/13	1.93 (0.84–4.46)	0.123
> 1/2						
≤ 0.16	13/2	1		12/1	1	
> 0.16	15/3	2.10(0.30-14.48)	0.453	16/5	4.83 (0.51–45.89)	0.171

HR*: adjusted by Age, Histological grade, FIGO stage, Depth of myometrial invasion, Lymph node metastasis, Menopause; FIB, fibrinogen;

CI, Confidence interval; HR, hazard ratio; NA, Not suitable for analysis.

D-dimer	Overall survival			Recurrence-free survival		
	Total/Dead	HR*(95% CI)	*P* value	Total/Recurrence	HR*(95% CI)	*P* value
Lymph node metastasis						
No						
≤ 0.16	219/3	1		213/10	1	
> 0.16	98/10	5.03(1.32–19.22)	**0.018**	104/15	2.32 (1.01–5.30)	**0.047**
Yes						
≤ 0.16	12/0	1		12/2		
> 0.16	8/2	1.00(0-9.6×10^{14})	1.000	8/3	NA	
Menopause						
No						
≤ 0.16	109/0			107/3	1	
> 0.16	41/1	NA		43/4	1.55 (0.28–8.47)	0.615
Yes						
≤ 0.16	122/3	1		118/9	1	
> 0.16	65/11	5.32(1.42–19.99)	**0.013**	69/14	1.96 (0.81–4.75)	0.137

HR*: adjusted by Age, Histological grade, FIGO stage, Depth of myometrial invasion, Lymph node metastasis, Menopause; FIB, fibrinogen;

CI, Confidence interval; HR, hazard ratio; NA, Not suitable for analysis.

Combined prognostic value of preoperative plasma fibrinogen and D-Dimer concentration in EC patients

To assess whether combination of preoperative plasma fibrinogen and D-Dimer concentration can improve prognostic prediction efficacy in EC patients, we further analyzed the effect of combining preoperative plasma fibrinogen and D-Dimer concentration on prognosis of EC. However, an abnormal result was observed in OS analysis which may be due to few death incidents in our study. Therefore, we performed RFS analysis in further study. Using patients with low fibrinogen and low D-Dimer levels as a reference group, patients with higher fibrinogen and higher D-Dimer concentration exhibited a significantly poorer RFS in both univariate (HR 8.66, 95% CI 2.84–26.35, $P = 0.0001$) and multivariate analysis (HR 5.89, 95% CI 1.88–18.50, $P = 0.002$). The effect on patient RFS was more evident in the patients with high fibrinogen and high D-Dimer concentration than in the patients with lower fibrinogen and higher D-Dimer concentration (HR 2.25, 95% CI 0.55–9.210, $P = 0.258$) or higher fibrinogen and lower D-Dimer concentration (HR 4.39, 95% CI 1.258–15.45, $P = 0.021$) (Table 7). Additionally, Kaplan–Meier analysis indicated that the patients with low fibrinogen and low D-Dimer concentration exhibited the longest RFS (log-rank $P = 1.3 \times 10^{-4}$, Fig. 2). All these data suggested that the combination of fibrinogen and D-Dimer concentration had a better efficacy in prognostic RFS of EC patients.

Table 7
Combination effect of FIB and D-dimer values on EC recurrence-free survival

Variables	Univariate		Multivariate*	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
low FIB values + low D-dimer values	1		1	
low FIB values + high D-dimer values	2.10(0.52–8.46)	0.295	2.25(0.55–9.21)	0.258
high FIB values + low D-dimer values	4.46(1.34–14.85)	**0.015**	4.39(1.25–15.45)	**0.021**
high FIB values + high D-dimer values	8.66(2.84–26.35)	**0.0001**	5.89(1.88–18.50)	**0.002**
P for trend		**0.001**		**0.017**

Multivariate*: adjusted by Age, Histological grade, FIGO stage, Depth of myometrial invasion, Lymph node metastasis, Menopause;

FIB, fibrinogen; CI, Confidence interval; HR, hazard ratio.

Discussion

Here, we found that patients with higher preoperative plasma fibrinogen or higher D-Dimer levels had significantly poorer prognosis, suggesting that preoperative plasma fibrinogen and D-Dimer levels may serve as independent prognostic factors for EC patients. Furthermore, combination of fibrinogen and D-Dimer significantly improved the prognosis prediction efficacy for RFS of EC patients.

It has been demonstrated that the coagulation/fibrinolytic systems are implicated in tumorigenesis, progression, and metastasis [9]. Abnormal activation of the coagulation/fibrinolytic system has been frequently identified in various cancers [2, 30]. Therefore, the degradation products of coagulation/fibrinolytic system have been used as biomarker of tumor load and prognosis [18, 26]. Recent researches demonstrated that fibrinogen and D-dimer are both dysregulated and implicated in cancer progress in many different types of cancers [7, 18, 26]. The prognostic values of D-dimer and fibrinogen have been investigated in various cancer types [17, 20, 23]. Previous studies reported that plasma D-dimer levels were markedly elevated and may predict the prognosis in patients with lung [1, 16], prostate [25] and colorectal carcinoma [3, 15]. These data collectively suggest that D-dimer concentration may be a potential biomarker for risk assessment and prognostication of cancer. Recently, a research reported that lower D-dimer levels was significantly associated with longer OS and RFS of EC patients treated with intensity-modulated radiation therapy [34]. Higher D-dimer level was also identified as an independent prognosticator in surgically treated EC patients [16]. In this study, we also assessed the associations of preoperative plasma D-dimer concentration with OS and RFS of EC patients. Consistent with previous findings [16, 34], our results demonstrated that higher preoperative plasma D-dimer levels were significantly associated with poorer prognosis of EC patients (Table 4). In addition, Kaplan-Meier curve analysis indicated that EC patients with higher preoperative plasma D-dimer levels had a significantly shorter OS and RFS (Fig. 1(C, D)).

Fibrinogen is identified as a major component of tumor stroma and has been demonstrated to be involved in proliferation, invasion, and metastasis of tumor by promoting tumor angiogenesis and supporting the sustained adhesion of tumor cells [22, 29]. Previous researches have demonstrated that the disruption of micro vessel resulted to accumulation of fibrinogen, which resulted in the activation of macrophages and monocytes and promoting the secretion of many cytokines and chemokines [13, 14]. Higher preoperative plasma fibrinogen level is an independent marker for impaired prognosis of colorectal cancer patients after curative resection [31], esophageal carcinoma [20] and penile cancer [21]. Previous reports showed that plasma fibrinogen level may be a useful biomarker in predicting outcomes of EC patients [12]. In this study, we found that higher plasma fibrinogen was significantly associated with poorer OS and RFS in EC patients (Table 4). Kaplan-Meier curve analysis demonstrated that EC patients with higher plasma fibrinogen levels had a significantly poorer OS and RFS (Fig. 1(A, B)).

In the stratified analyses, we found that higher preoperative plasma fibrinogen and D-dimer levels were significantly associated with poor prognosis in patients with older age, without lymph node metastasis, with depth of myometrial invasion and in post-menopausal status. These results indicated that the plasma fibrinogen and D-dimer concentration may be modulated by host characteristics through unknown mechanisms. However, the molecular mechanisms modulated plasma fibrinogen and D-dimer concentrations in cancer patients are still unclear. The detailed mechanisms should be investigated in the future.

To further identify the combined effects of plasma D-dimer and fibrinogen levels on EC patient's prognosis, we grouped the patients according to the levels of the two parameters. Interestingly, our results showed that patients with higher D-dimer levels and higher fibrinogen levels had a significantly worse RFS than patients with any one abnormal parameter. The results indicated that elevated plasma fibrinogen and D-dimer levels contributed to the poor RFS of EC patients synergistically. Previous researches have demonstrated that elevated fibrinogen and D-dimer levels are correlated to the tumor hypercoagulability. Abnormal activations of the coagulation/fibrinolytic system, especially plasma dimerized plasmin fragment D (D-dimer) and fibrinogen, have been frequently identified in cancer patients [2, 30]. In this study, our results have suggested that combination of fibrinogen and D-Dimer significantly improved the prognosis prediction efficacy for RFS of EC patients.

In conclusion, our findings suggested that preoperative plasma fibrinogen and D-Dimer concentration may serve as useful biomarkers for prognosis stratification of EC patients. In addition, combination of fibrinogen and D-Dimer significantly improved the prognosis prediction efficacy for RFS of EC patients. Therefore, plasma fibrinogen/D-Dimer may serve as a potential biomarker to predict EC prognosis.

Declarations

Acknowledgments

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Disclosure statement

The authors declare that they have no conflicts of interest.

Author Contributions

WLX and WYY wrote the manuscript. YXJ, HJR, SJY, WXJ, YXT, WY, YGQ, LYF, YZ, BDK and SMH performed some of the lab work and data collection. WLX and WYY supported the overall data analysis and provided constructive discussion. BDK, ZJJ and YSH conceived and designed the study. All authors read and approved the final manuscript.

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Figures

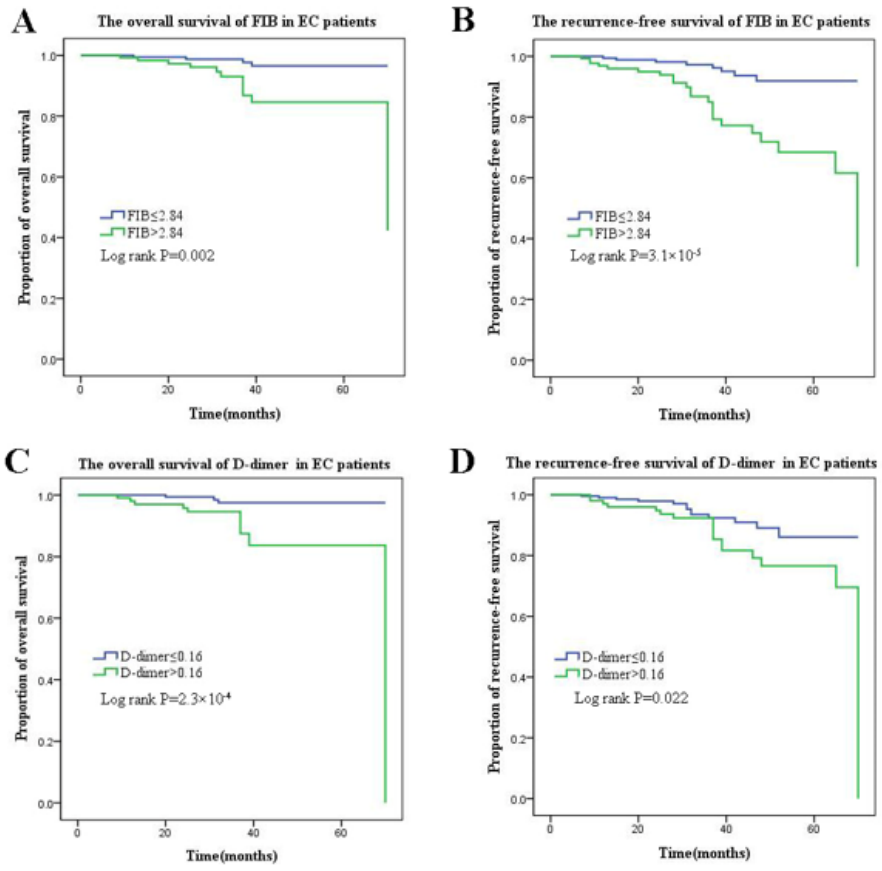

Figure 1

Kaplan-Meier curves of overall survival and recurrence-free survival analyses in EC patients with FIB and D-dimer. FIB, fibrinogen.

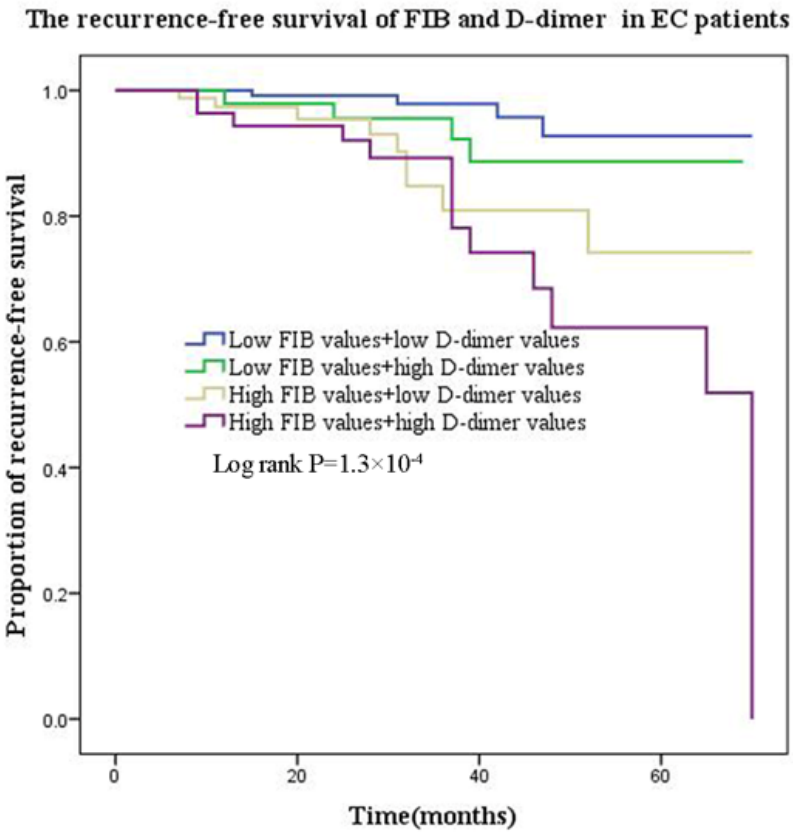

Figure 2

Combined effect of FIB and D-dimer levels on recurrence-free survival of EC patients using the Kaplan-Meier curves. FIB, fibrinogen.