The significance of plasma D-dimer level in predicting high risk factors of endometrial cancer

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Background: Activated clotting-fibrinolytic system is associated with poor outcome of cancer patients. This retrospective study aimed to evaluate the significance of plasma D-dimer level in predicting high risk factors of endometrial cancer (EC) patients.

Methods: Total 176 EC patients who underwent radiotherapy between January 2018 and June 2019 at Shanghai First Maternity and Infant Hospital were retrospectively analyzed. Their preoperative and postoperative plasma D-dimer levels were measured as routine assessment in our hospital, and analyzed for their association with clinicopathological data retrieved from medical records of the patients.

Results: High risk group had significantly higher 1st day postoperative D-dimer levels. The 1st day postoperative D-dimer predicted higher grade EC with the specificity of 63.7% and the sensitivity of 63.4%; predicted late stage EC with the specificity of 83.7% and the sensitivity of 58.6%; predicted deeper myoinvasion of EC with the specificity of 84.9% and the sensitivity of 43.3%; predicted lymphovascular space invasion positive EC with the specificity of 84.0% and the sensitivity of 50.0%; predicted lymph node metastasis of EC with the specificity of 50.9% and the sensitivity of 100%; and predicted cervical invasion of EC with the specificity of 82.1% and the sensitivity of 65.0%.

Conclusions: Increased postoperative plasma D-dimer levels accurately predicted high risk factors in patients with EC.

Keywords: Endometrial cancer (EC); D-dimer; risk factor; predict

Introduction

The cases of endometrial cancer (EC) diagnosed are increasing (1,2). Surgery is still the standard treatment for early-stage EC (3). However, treatment strategies would be different for EC patients with different incidence of recurrence after surgery. Based on FIGO stage, grade and histotype, EC patients are divided into low risk and high risk groups for the risk of tumor recurrence (4). Biomarkers could help identify people with high risk of cancer (5). Therefore, it is urgent to develop new reliable biomarkers to stratify EC patients into risk categories for individualized therapy (6).

D-dimer is involved in coagulation activation and has been applied for the diagnosis of venous thromboembolism (VTE) (7). In addition, D-dimer levels increase in several kinds of cancer, and correlate with poor prognosis and resistance to treatment (8). However, a recent study suggested that D-dimer levels may not be a promising independent prognostic factor for EC (9). To further investigate the significance of plasma D-dimer in the prediction of high risk group of EC patients, in this

retrospective study we analyzed the correlation of preoperative and postoperative plasma D-dimer levels with clinicopathological data of EC patients.

Methods

Patients and procedures

This retrospective study was approved by the Research Ethics Committee of Shanghai First Maternity and Infant Hospital. Demographic and clinical data were collected from medical records of 176 EC patients who underwent radiotherapy between January 2018 and June 2019 at Shanghai First Maternity and Infant Hospital (Shanghai, China). The inclusion criteria included: EC diagnosis pathologically confirmed, no previous radiotherapy or chemotherapy, complete clinical data in medical record, and clinical staging was I–IV. The exclusion criteria included: thromboembolism in previous three months, using anticoagulation drugs, history of congenital thrombophilia, anticoagulant treatment, pregnancy, or stroke in previous six months, and cancer metastasis at the diagnosis. All procedures (total hysterosalpingo-oophorectomy and complete bilateral lymphadenectomy) were performed laparoscopically by the same experienced surgeon.

Biochemical parameters

After a 10-hour overnight fast, blood samples were collected from participants, and plasma was then analyzed using second-generation latex immunoassay kit for D-dimer on Sysmex CS-5100 (Siemens Diagnostics, Erlangen, Germany). The standard cut-off value of D-dimer in our hospital was 0.55 mg/L. Platelet count levels were determined with an autoanalyzer (Sysmex XE-2100, Kobe, Japan).

Diagnosis of deep vein thrombosis and pulmonary embolism

An experienced ultrasonographist performed the compression ultrasonography according to standard procedures (Grey scale, B-mode, Color Doppler) with a high-end ultrasound scanner (Philips HD15 Ultrasound, USA) before and after surgery. If the patients had clinical signs of deep vein thrombosis, additional compression ultrasonography was performed. Pulmonary embolism was diagnosed based on computed tomography of the chest.

All Computed tomography pulmonary angiograms were analyzed by two experienced radiologists.

Statistical analysis

Data were analyzed by t-test, analysis of variance, Mann-Whitney U test, and Pearson's correlation analysis. Univariate and multivariate analyses based on Cox hazard model was used to determine prognostic factors. Receiver operating characteristic (ROC) curve was used to calculate cut-off value. Significance was indicated at P<0.05.

Results

Correlations between preoperative D-dimer plasma levels and clinicopathological parameters

Total 176 EC patients were included and their clinicopathologic data were collected (*Table 1*). The average preoperative D-dimer level was 0.42 mg/L (range, 0.07–3.31 mg/L), and the first day postoperative D-dimer level was 1.50 mg/L (range, 0.11–9.43 mg/L). The preoperative plasma D-dimer level was below the normal level (0.55 mg/L) in 145/176 (82.39%) patients and was above the normal level in 31/176 (17.61%) patients. The median age was 54.6 years, and median body mass index (BMI) was 25.37 kg/m^2 for all patients. Higher D-dimer level showed significant correlation with older age (P=0.0067). There was no significant association of preoperative plasma D-dimer level with platelet level (P=0.3846) or BMI (P=0.9537).

The first day postoperative D-dimer levels predicted tumor progression

The associations between clinicopathologic characteristics and preoperative and postoperative plasma D-dimer levels were presented in *Table 2*. Compared to low-grade group, the first day postoperative D-dimer levels were significantly higher in high-grade group (P=0.0135; *Figure 1A*). Compared to early-stage group, the first day postoperative D-dimer levels were significantly higher in late-stage group (P<0.0001; *Figure 1B*). Compared to lymph node metastasis group, the first day postoperative D-dimer levels were significantly higher in non-LN involvement group (P=0.0397; *Figure 1C*). Compared to the <1/2 myoinvasion group, the first day postoperative D-dimer levels were significantly higher in deep myoinvasion group (P=0.0003;

Table 1 Clinical-pathological features

Characteristic	Subgroup	Number (n=176)	Percent
Age (Y)	Median	54.63068182	
	Range	26–78	
	<60	117	66.48%
	≥60	59	33.52%
Body mass index (BMI) (kg/m^2)	Median	25.36704545	
	Range	15.6–42.19	
	<25	99	56.25%
	≥25	77	43.75%
D-dimer (mg/L)	Median	0.4175	
	Range	0.07–3.31	
	D-dimer <0.55	145	82.39%
	D-dimer ≥0.55	31	17.61%
Pathological type	Type 1	158	89.77%
	Type 2	17	9.66%
FIGO stage	I	147	83.52%
	II	14	7.95%
	III–IV	15	8.52%
Tumor differentiation	G1	135	76.70%
	G2–3	41	23.30%
Myometrial infiltration	<1/2	146	82.95%
	≥1/2	30	17.05%
Cervical stromal invasion	Positive	29	16.48%
	Negative	148	84.09%
Lymphovascular space invasion	Positive	20	11.36%
	Negative	156	88.64%
Peritoneal cytology	Positive	0	0.00%
	Negative	176	100.00%
Lymph node metastasis	Positive	7	3.98%
	Negative	169	96.02%
Preoperative platelet	Median	257.2306818	
	Range	119–530.1	
Preoperative D-dimer (mg/L)	Median	0.4175	
	Range	0.07–3.31	
	<0.5	140	79.55%
	≥0.5	37	21.02%

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Subgroup	Number (n=176)	Percent
Postoperative D-dimer (mg/L)	Median	1.50	
	Range	0.11–9.43	
	<0.5	36	20.45%
	≥0.5	140	79.55%
VTE	Positive	11	
	Negative	165	
Microsatellite stabilization	Stable	112	63.64%
	Instability	34	19.32%
Operation time (minutes)	Median	152.5965909	
	Range	75–170	
Intraoperative blood loss (mL)	Median	86.07954545	
	Range	10–1,300	

VTE, venous thromboembolism.

Figure 1D). Compared to lymphovascular space invasion negative group, the first day postoperative D-dimer levels were significantly higher in lymphovascular space invasion positive group (P=0.0345; *Figure 1E*). Moreover, the 1st day postoperative D-dimer level was significantly correlated with preoperative D-dimer level (R^2=0.1795, P<0.0001) (*Figure 1F*).

ROC curve analysis showed that optimal cut-off value for the 1st day postoperative D-dimer level was 1.25 mg/L for grade 2–3, 2.04 mg/L for stage III–IV, 2.205 mg/L for deep myoinvasion, 2.205 mg/L for lymphovascular space invasion, 1.07 mg/L for lymph node metastasis, and 2.04 mg/L for cervical invasion (*Figure 2A,B,C,D,E,F*). In addition, D-dimer predicted higher grade EC with the specificity of 63.7% and the sensitivity of 63.4% (AUC 0.662, P=0.002); D-dimer predicted late stage EC with the specificity of 83.7% and the sensitivity of 58.6% (AUC 0.754, P<0.001); D-dimer predicted deeper myoinvasion (≥1/2 myoinvasion) of EC with the specificity of 84.9% and the sensitivity of 43.3% (AUC 0.674, P=0.003); D-dimer predicted lymphovascular space invasion positive EC with the specificity of 84.0% and the sensitivity of 50.0% (AUC 0.683, P=0.008); D-dimer predicted lymph node metastasis of EC with the specificity of 50.9% and the sensitivity of 100% (AUC 0.78, P=0.012); D-dimer predicted cervical invasion of EC with the specificity of 82.1% and the sensitivity of 65.0% (AUC 0.742, P=0.012).

Changes in preoperative and postoperative D-dimer levels were correlated with VTE events

ROC curve showed significant association of D-dimer level with thrombus burden, and optimal cut-off values of D-dimer were 0.285 and 1.4 mg/L to predict VTE event. Notably, the preoperative D-dimer level was significantly affected by BMI, but not by the age and preoperative platelet. Preoperative D-dimer level was significantly correlated with 1st postoperative day D-dimer level (P<0.0001, *Figure 3*).

Discussion

EC most commonly presents with post-menopausal bleeding, and long-term bleeding may cause the abnormality of coagulation system. It is known that coagulation and fibrinolysis are activated in cancers, including gynecological cancers (10). In addition, VTE is a common complication in cancer patients and is listed as an important cause of cancer related death (11-13).

Plasma D-dimer is regarded as an important biomarker of fibrinolysis. The imbalance of the coagulation system is implicated in tumorigenesis (14,15). It is proposed that cancer patients are in subclinical hypercoagulable condition, and fibrinolysis promotes tumor angiogenesis, leading to poor prognosis and even death. A recent study reported

Table 2 Association between D-dimer levels and clinicopathological features in patients with endometrial cancer (n=176)

| Influencing factor	Subgroup	Pre-operative			1st post-operative day		
		D-dimer <0.55 mg/L	D-dimer ≥0.55 mg/L	P value	D-dimer <0.55 mg/L	D-dimer ≥0.55 mg/L	P value
Age (Y)	<60	99 (84.6%)	18 (15.4%)	0.274	30 (25.6%)	87 (74.4%)	0.016*
	≥60	46 (78%)	13 (22%)		6 (10.2%)	53 (89.8%)	
Body mass index (BMI) (kg/m^2)	<25	83 (83.8%)	16 (16.2%)	0.431	17 (17.2%)	82 (82.8%)	0.221
	≥25	61 (79.2%)	15 (20.8%)		19 (24.7%)	58 (75.3%)	
FIGO stage	I–II	122 (83%)	25 (27%)	0.634	36 (24.5%)	111 (75.5%)	0.001*
	III–IV	23 (79.3%)	6 (20.7%)		0 (0%)	29 (100%)	
Tumor differentiation	G1	108 (80%)	27 (20%)	0.097	34 (25.2%)	101 (74.8%)	0.002*
	G2–3	37 (90.2%)	4 (9.8%)		2 (4.9%)	39 (95.1%)	
Myometrial infiltration	<1/2	119 (81.5%)	27 (18.5%)	0.352	35 (24%)	111 (76%)	0.05*
	≥1/2	26 (86.7%)	4 (13.3%)		1 (3.3%)	29 (96.7%)	
Cervical stromal invasion	Negative	129 (82.7%)	27 (17.3%)	0.484	35 (22.4%)	121 (77.6%)	0.053
	Positive	16 (80%)	4 (20%)		1 (5%)	19 (95%)	
Lymphovascular space invasion	Negative	127 (81.4%)	29 (18.6%)	0.274	35 (22.4%)	121 (77.6%)	0.053
	Positive	18 (90%)	2 (10%)		1 (5%)	19 (95%)	
Lymph node metastasis	Negative	140 (82.8%)	29 (17.2%)	0.357	36 (21.3%)	133 (78.7%)	0.195
	Positive	5 (71.4%)	2 (28.6%)		0 (0%)	7 (100%)	
VTE	Negative	137 (83%)	28 (17%)	0.385	36 (21.8%)	129 (78.2%)	0.074
	Positive	8 (72.7%)	3 (27.3%)		0 (0%)	11 (100%)	
CA125 (U/mL)	<35	122 (84.1%)	23 (15.9%)	0.187	32 (22.1%)	113 (77.9%)	0.185
	≥35	23 (74.2%)	8 (25.8%)		4 (12.9%)	27 (87.1%)	
Pathological type	Type I	129 (81.6%)	29 (18.4%)	0.445	35 (22.2%)	123 (77.8%)	0.08
	Type II	16 (88.9%)	2 (11.1%)		1 (5.6%)	17 (94.4%)	
Platelet count (×10^9/L)	<320	126 (84.6%)	23 (15.4%)	0.027	32 (21.5%)	117 (78.5%)	0.308
	≥320	18 (66.7%)	9 (33.3%)		4 (14.8%)	23 (85.2%)	
MS	MSS	120 (84.5%)	22 (15.5%)	0.131	31 (21.8%)	111 (78.2%)	0.355
	MSI	25 (73.5%)	9 (26.5%)		5 (14.7%)	29 (85.3%)	

VTE, venous thromboembolism.

that D-dimer may predict postoperative recurrence and prognosis in patients with colorectal cancer metastasis. However, whether plasma D-dimer level could indicate postoperative recurrence and prognosis of EC patients remains unclear.

Currently, there are no valid noninvasive diagnostic methods available for EC. Biomarkers for EC would be invaluable for screening high-risk women, detecting primary and recurrent disease, and preoperative stratification of patients as high-risk and low-risk categories for personalized therapies (16).

Cancer-associated thrombosis could threaten the life of patients, and it is suggested that targeting the coagulation or fibrinolysis system could alleviate cancer progression (17). In most cancers, high D-dimer level usually indicated advanced cancer stage and increased risk
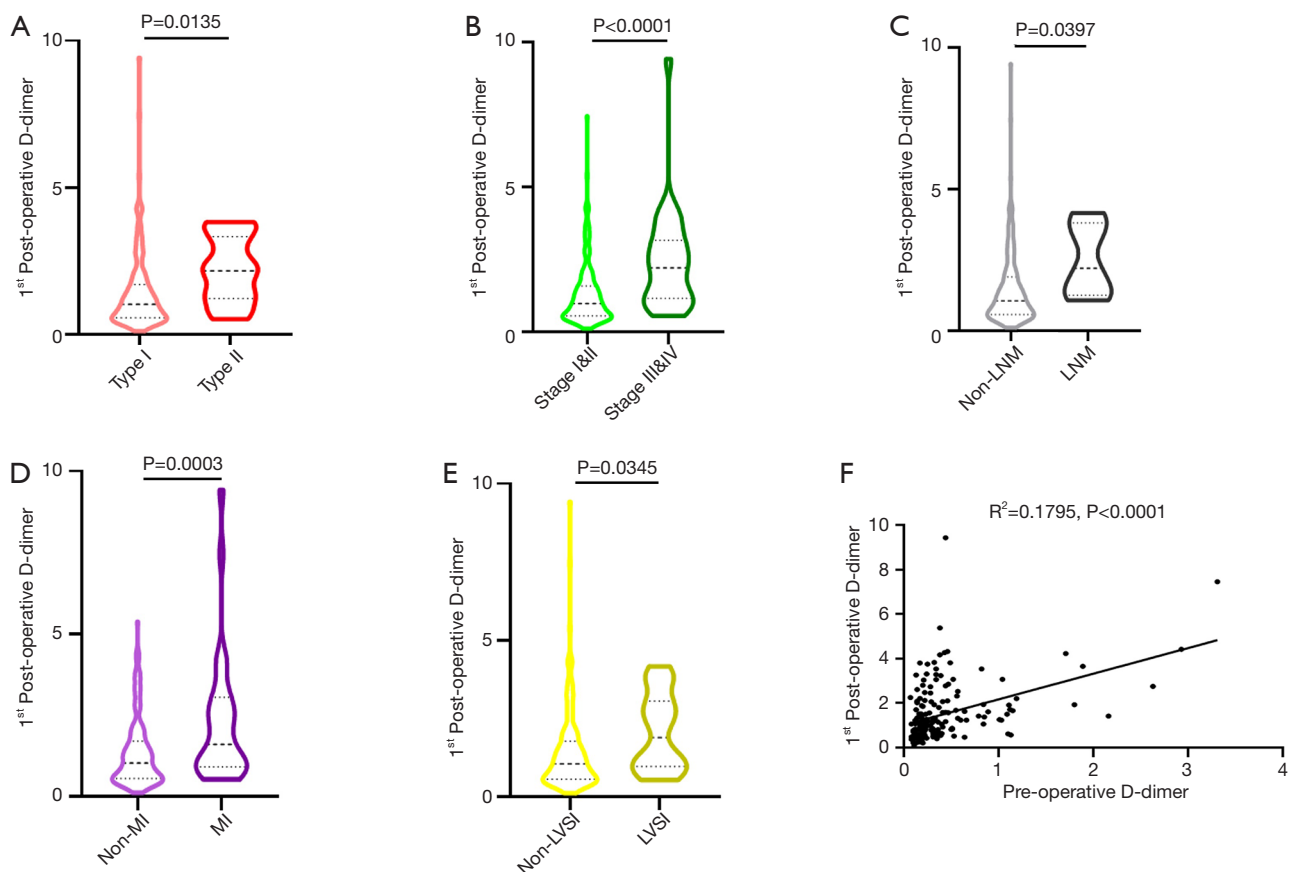
Figure 1 The association between 1st postoperative D-dimer level and clinicopathological parameters of EC patients. (A) Compared to low-grade group, high-grade group showed significantly higher the first day postoperative D-dimer levels (P=0.0135). (B) Compared to early-stage group, late-stage group showed significantly higher the first day postoperative D-dimer levels (P<0.0001). (C) Compared to lymph node metastasis group, non-LN involvement group had significantly higher the first day postoperative D-dimer levels (P=0.0397). (D) Compared to <1/2 myoinvasion group, the deep myoinvasion group had significantly higher the first day postoperative D-dimer levels (P=0.0003). (E) Compared to lymphovascular space invasion negative group, lymphovascular space invasion positive group had significantly higher the first day postoperative D-dimer levels (P=0.0345). (F) 1st day post-operative D-dimer showed significant correlation with pre-operative D-dimer (R2=0.1795, P<0.0001). EC, endometrial cancer.

of death (18). High D-dimer level is associated with the progression and metastasis of gastric cancer, esophageal cancer, lung cancer, ovarian cancer, and nasopharyngeal carcinoma (19-22). Furthermore, plasma D-dimer level could evaluate the response to chemotherapy in colorectal cancer patients (23).

In present study, we analyzed the association of preoperative and postoperative plasma D-dimer levels with clinicopathological data of EC patients who had undergone surgery to treat EC. We found that the 1st day postoperative D-dimer level predicted higher grade EC with the specificity of 63.7% and the sensitivity of 63.4%; predicted late stage EC with the specificity of 83.7% and

the sensitivity of 58.6%; predicted deeper myoinvasion of EC with the specificity of 84.9% and the sensitivity of 43.3%; predicted lymphovascular space invasion positive EC with the specificity of 84.0% and the sensitivity of 50.0%; predicted lymph node metastasis of EC with the specificity of 50.9% and the sensitivity of 100%; and predicted cervical invasion of EC with the specificity of 82.1% and the sensitivity of 65.0%. Our results suggest that 1st day postoperative plasma D-dimer levels could predict high risk factors for EC recurrence such as higher grade, late stage, deeper myoinvasion, lymphovascular space invasion, lymph node metastasis and cervical invasion. More importantly, ROC analysis showed that postoperative
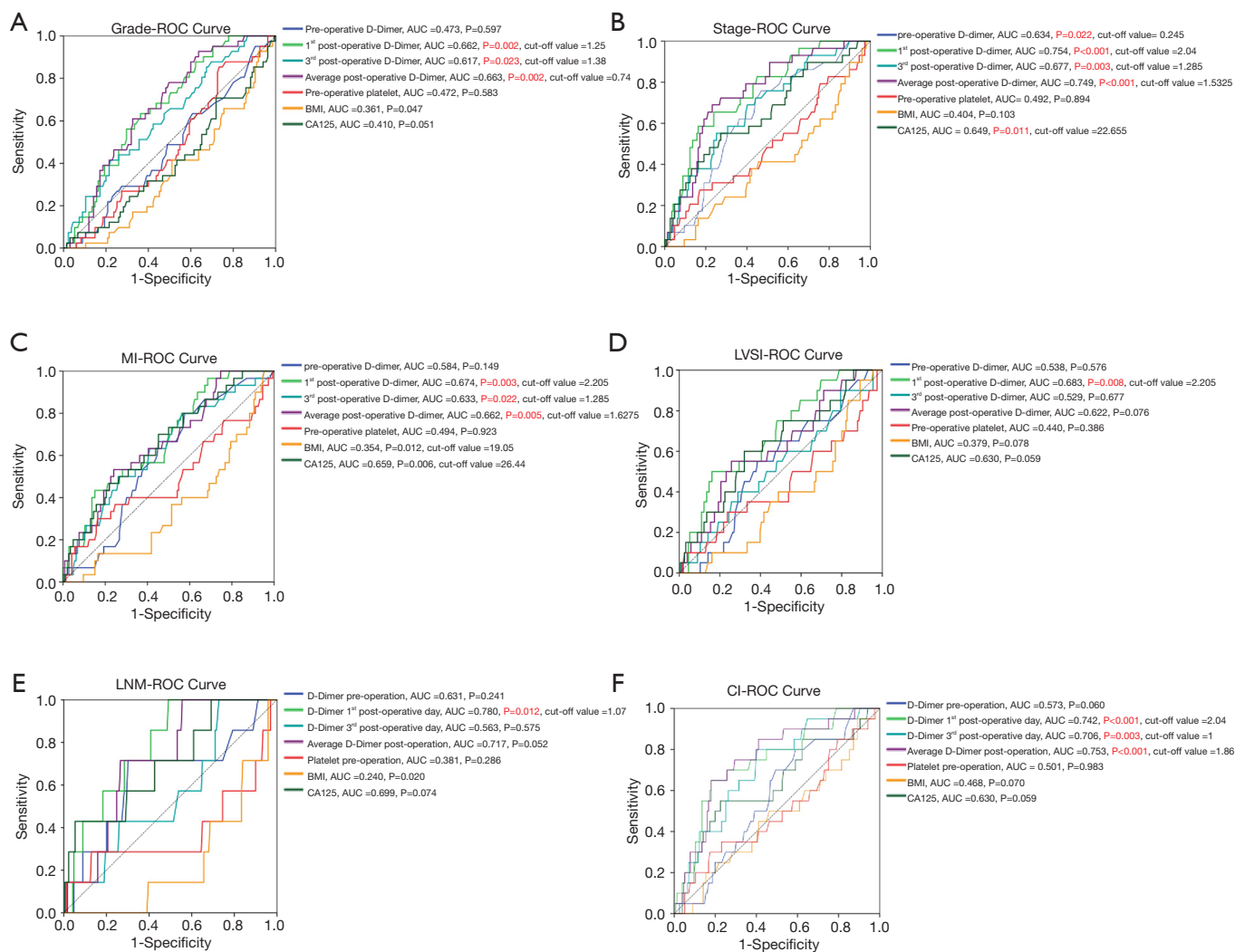
Figure 2 Optimized cut-off of the 1st day postoperative D-dimer levels for high risk of EC patients. (A) ROC curve for higher grade of EC showed that the optimal cut-off value for the 1st postoperative D-dimer was 1.25 mg/L (P=0.002). (B) ROC curve for higher stage of EC showed that the optimal cut-off value for the 1st postoperative D-dimer was 2.04 mg/L (P<0.001). (C) ROC curve for deep myoinvasion of EC showed that the optimal cut-off value for the 1st postoperative D-dimer was 2.205 mg/L (P=0.003). (D) ROC curve for lymphovascular space invasion of EC showed that the optimal cut-off value for the 1st postoperative D-dimer was 2.205 mg/L (P=0.008). (E) ROC curve for lymph node metastasis of EC showed that the optimal cut-off value for the 1st postoperative D-dimer was 1.07 mg/L (P=0.012). (F) ROC curve for cervical metastasis of EC showed that the optimal cut-off value for the 1st postoperative D-dimer was 2.04 mg/L (P<0.001). EC, endometrial cancer; ROC, receiver operating characteristic.

D-dimer level could be a better high-risk factor prediction than common tumor marker CA125 in EC patients. However, the accuracy of D-Dimer in the stratification of EC patients into risk categories need be confirmed in further large-scale and multi-center studies.

In conclusion, the activation of fibrinolysis system in cancer patients is an unfavorable clinical sign. As a degradation product of fibrin, increased postoperative plasma D-dimer level may be used to predict high risk of recurrence in EC patients.
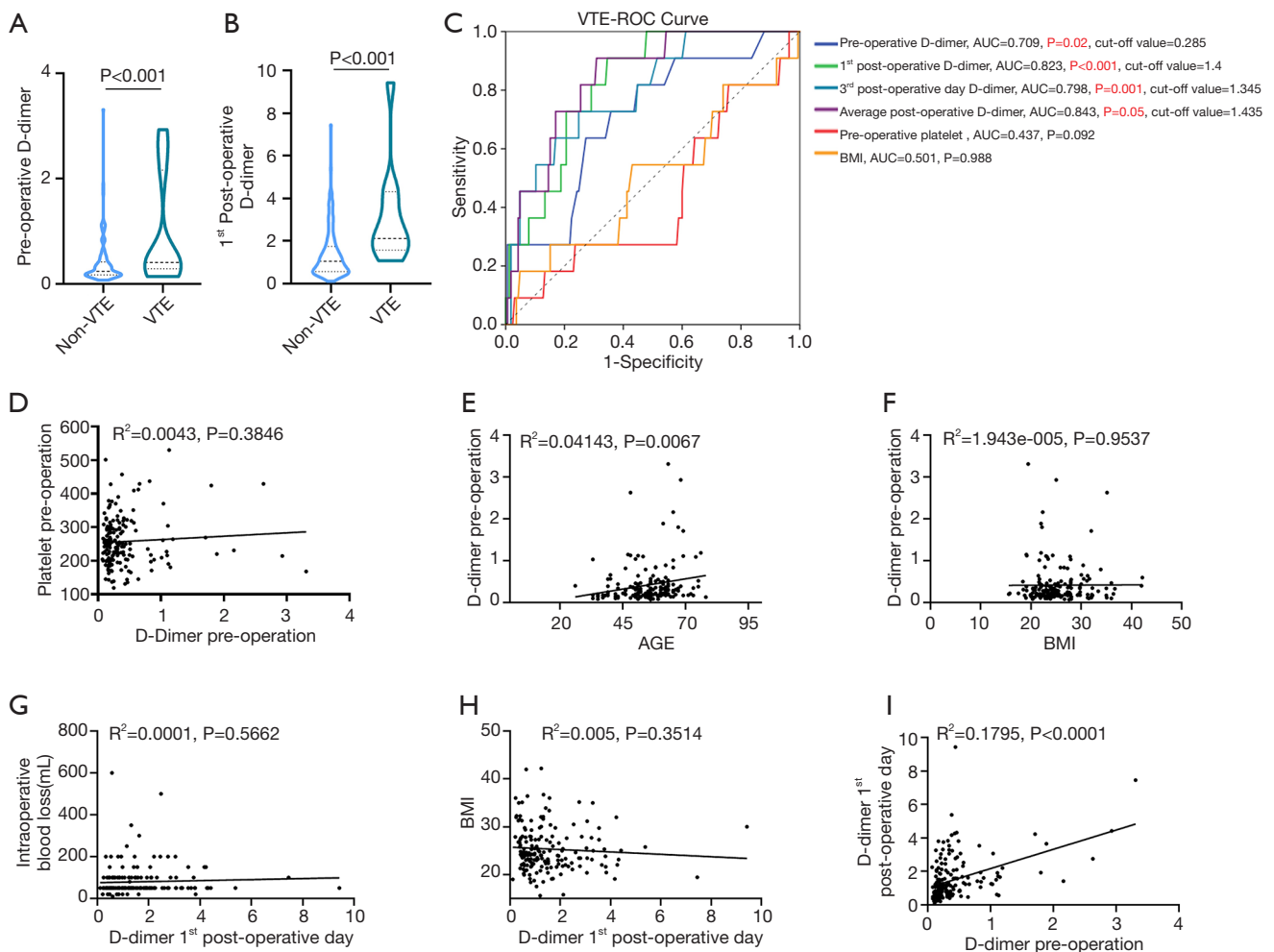
Figure 3 The relationship of preoperative and postoperative D-dimer levels with VTE events. (A) Compared to non-VTE patients, VTE patients showed significantly higher preoperative D-dimer levels (P<0.001). (B) Compared to non-VTE patients, VTE patients showed significantly higher the first day postoperative D-dimer levels (P<0.001). (C) Optimized cut-off was determined for preoperative and postoperative D-dimer levels using standard ROC curve analysis. (D,E,F) Preoperative D-dimer showed no correlation with preoperative platelet, body mass index and age. (G,H) 1st day postoperative D-dimer showed no correlation with preoperative body mass index and intraoperative blood loss. (I) 1st day postoperative D-dimer showed significant correlation with preoperative D-dimer (R^2=0.1795, P<0.0001). VTE, venous thromboembolism; ROC, receiver operating characteristic.

Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Research Ethics Committee of Shanghai First Maternity and Infant Hospital. Individual informed consent was waived due to the retrospective nature of the study.

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