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ORIGINAL RESEARCH

The Association Between D-Dimer Levels and Recurrence in Patients with Early-Stage Cervical Cancer after Surgical Treatment

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Purpose: This study was conducted to analyze the relationship between plasma D-dimer levels and the risk of recurrence after surgical treatment in patients with early-stage cervical cancer (CC).

Methods: In this cohort study, 888 participants with early-stage CC undergoing surgical treatment in Fujian Cancer Hospital between June 2016 and December 2019 were identified. Univariate logistic regression was used to screen confounding factors affecting the recurrence of early CC after surgical treatment. Variables significantly associated with the recurrence of early CC after surgical treatment were confounding factors. Univariate and multivariate logistic regression models were established to explore the association between D-dimer levels and the risk of recurrence of early CC after surgical treatment. ORs and 95% CIs were calculated.

Results: The end of follow-up was when CC recurred or 3 years after surgery. In sum, 80 patients suffered CC recurrence, accounting for 9% of all participants. The risk of recurrence was elevated in CC patients from the elevated group (EG), with an adjusted OR of 2.16 (95% CI 1.28–3.62). The risk of recurrence was increased in the EG in patients with cervical squamous cell carcinoma undergoing surgery in the adjusted model (OR 3.58, 95% CI 1.02–12.89). As for cervical adenocarcinoma patients, the increased risk of recurrence was identified in patients from the EG (OR 1.87, 95% CI 1.01–3.48).

Conclusion: High levels of D-dimer were associated with increased recurrence risk of CC in patients at the early stage of surgical treatment.

Keywords: D-dimer, cervical cancer, surgical treatment, recurrence

Introduction

Cervical cancer (CC) is the fourth–most commonly diagnosed malignant tumor in women and one of the leading causes of cancer-related death in women.[1] More than 500,000 women are diagnosed with CC each year, and more than 300,000 die.[2] With the development of medical technology, effective screening tools have allowed more than a third of CC cases to be diagnosed at an early stage.[3] For the treatment of early-CC patients, surgical treatment has always been recommended, but patients are still at high risk of recurrence after surgical treatment, and the risk of recurrence is different based on the histological differences in CC.[4] Evidence has indicated that the risk of recurrence in CC patients who receive no further treatment after hysterectomy is 44% in cervical adenocarcinoma and 28% in cervical squamous cell carcinoma.[5] In addition, CC patients have no effective treatments after recurrence, and patients with recurrence showed a significantly higher risk of mortality than those without.[6] Early identification of patients with high recurrence probability and implementation of intensive treatment may greatly improve the survival of patients.[7]

A hypercoagulable state is common in tumors, which is not only closely related to thrombosis but also tumor progression.[8] D-dimer, a degradation product of fibrin that is produced when cross-linked fibrin is degraded by

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fibrinolytic activity induced by plasmin, is a key predictor of coagulation dysfunction.[9] Elevated plasma D-dimer levels have been reported in different malignancies, such as gastric, colorectal, cervical, breast, and esophageal cancer.[10,11] Increasing evidence is indicating that high D-dimer levels are related to poor prognosis of cancer patients and serve as an effective predictor of the prognosis of these patients.[12] High levels of D-dimer in plasma have been detected in CC patients before treatment, and plasma D-dimer has been reported to be associated with CC tumor stage and grade, demonstrating the potential clinical value of plasma D-dimer as a diagnostic and prognostic marker of CC.[13] However, the independent prognostic significance of plasma D-dimer in CC patients remains largely unknown.

The aim of this study was to analyze the relationship between plasma D-dimer levels and the risk of recurrence after surgical treatment in patients with early CC, cervical squamous cell carcinoma, or cervical adenocarcinoma. Subgroup analysis was performed concerning age, tumor size, depth of interstitial infiltration, and surgical method.

Methods

Study Design and Population

This cohort study enrolled 1062 patients with early-stage CC undergoing surgical treatment at Fujian Cancer Hospital between June 2016 and December 2019. The inclusion criteria were age ≥18 years and diagnosed with CC at International Federation of Gynecology and Obstetrics (FIGO) stage IB–IIA. The exclusion criteria were: 1) incomplete clinical information; 2) rare histological subtypes, including mesonephric carcinoma, cervical clear-cell carcinoma, small-cell carcinoma of the cervix, mixed neuroendocrine histology, and endometrioid cervical carcinoma; 3) complicated by other malignant tumors or history of other malignant tumors; 4) no surgical treatment; 5) history of receiving chemotherapy or radiation therapy for other diseases; and 6) no data on D-dimer levels. This study was approved by the Institutional Review Board of the Clinical Oncology School of Fujian Medical University Fujian Cancer Hospital. The need for written informed consent was waived by the board due to the retrospective nature of the study. All procedures were performed in accordance with the relevant guidelines and regulations.

Potential Covariates

Age, diabetes (yes or no), hypertension (yes or no), other diseases (yes or no), hemoglobin (g/L), red blood cells (RBCs; 10^{12}/L), white blood cells (WBCs; 10^9/L), platelets (10^9/L), neutrophils (10^9/L), lymphocytes (10^9/L), monocytes (10^9/L), eosinophils (10^9/L), basophils (10^9/L), mean platelet volume (MPV; fL), RBC distribution width (RDW; %), alanine aminotransferase (ALT; U/L), aspartate aminotransferase (AST; U/L), γ-glutamyl transpeptidase (GGT) (U/L), alkaline phosphatase (ALP; U/L), lactate dehydrogenase (LDH; U/L), total bilirubin (TBil; μmol/L), direct bilirubin (DBil; μmol/L), indirect bilirubin (IBil; μmol/L), total protein (g/L), albumin (g/L), globulin (g/L), prothrombin time (PT; seconds), activated partial thromboplastin time (APTT; seconds), thrombin time (TT; seconds), fibrinogen (<4 g/L or ≥4 g/L), squamous cell carcinoma antigen (SCC-Ag; <4 ng/mL or ≥4 ng/mL), FIGO stage (I or II), tumor size (<2 cm, 2–4 cm, or ≥4 cm), tumor stage (I, II, or III), positive lymph nodes (yes, no or unknown), number of lymph nodes removed, depth of interstitial infiltration (central, inside, outside, or no), infiltration of lymphatic vascular space (yes or no), paracentric tissue infiltration (yes or no), lymphatic metastasis (yes or no), paraaortic metastasis (>5 or ≤5), positive incisal margin (yes or no), preoperative tapering (yes or no), surgical method (laparoscopy, laparotomy, or laparotomy plus laparoscopy), surgery length (hours), sentinel lymph-node biopsy (yes or no), and body mass index (BMI; normal, underweight, overweight, or obese) were the variables analyzed in this study.

Main and Outcome Variables

D-dimer was the main variable, which was detected at admission. D-dimer levels were divided into an elevated group (EG; ≥0.5 mg/L) and a normal group (NG; <0.5 mg/L). Outpatient follow-up was performed once every 3–6 months within the first 2 years from treatment and once every 6–12 months from the beginning of the third year. The end of follow-up was when CC recurred or 3 years after surgery.

Statistical Analysis

The normality of quantitative data was tested by skewness and kurtosis methods, and the homogeneity of variance was tested by Levene's test. Normal distribution measurement data are presented as means ± SD. Student's *t* test was used for comparison between groups with homogeneity of variance, and Satterthwaite's *t* test was used for heterogeneity of variance. Abnormal distribution measurement data are presented as medians and quartiles (Q_1–Q_3), and Wilcoxon's rank-sum test was used for comparison between groups. Enumeration data are presented as the number and percentage of cases, and χ^2 or Fisher's exact test was used for comparison between groups. Missing values are shown in Supplementary Table 1, and sensitivity analysis of data before and after interpolation is detailed in Supplementary Table 2. Univariate logistic regression was used to screen the confounding factors affecting the recurrence of early CC after surgical treatment. Univariate and multivariate logistic regression models were established to explore the association between D-dimer and the risk of recurrence of early CC after surgical treatment. Variables significantly associated with the recurrence of early CC after surgical treatment were confounding factors and adjusted in the multivariate logistic regression model. This study examined three populations: those with early CC, cervical squamous cell carcinoma, or cervical adenocarcinoma. Subgroup analysis was stratified by age, tumor size, depth of interstitial infiltration, and surgical method. Odds ratio (OR) and confidence interval (CI) were calculated. R version 4.3.1 (2023–06-16 ucrt) was used for statistical analysis. $P<0.05$ was considered statistically significant.

Results

Comparisons of Characteristics of CC Patients With/out Recurrence

In total, 1062 patients with early CC receiving surgical treatment were recruited from Fujian Cancer Hospital. Those with incomplete clinical data (n=90), rare histological classification (n=28), current or prior presence of other malignancies (n=15), no surgical treatment (n=7), prior chemotherapy or radiotherapy for other diseases (n=12), and with no D-dimer data available (n=22) were excluded. Finally, 888 participants were included. The process of participant screening is exhibited in Figure 1.

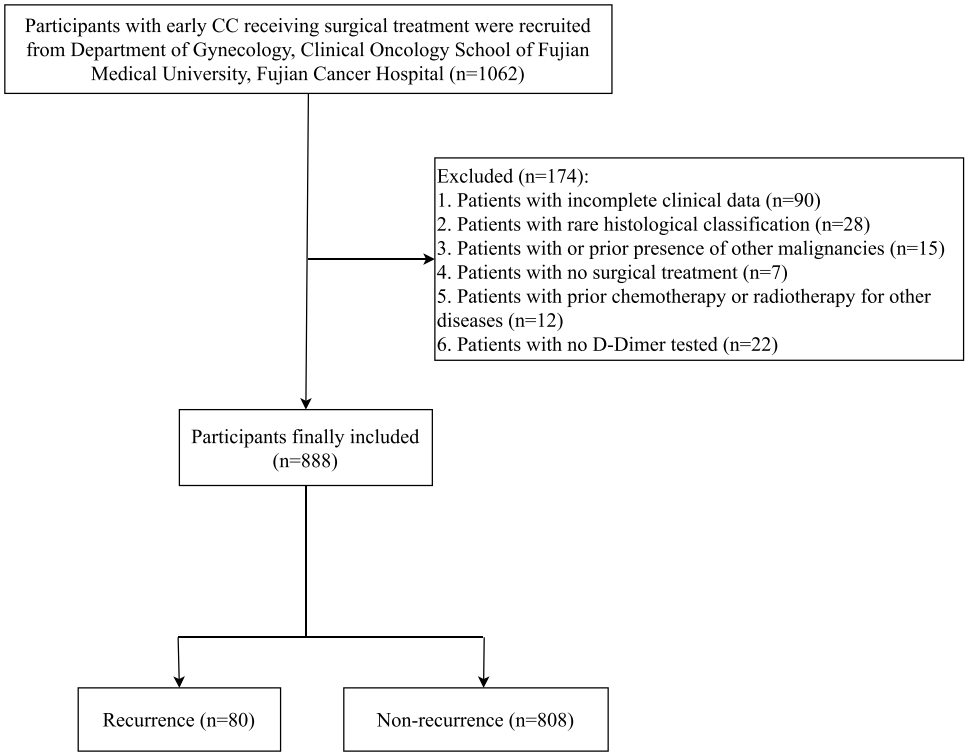

Figure 1 Screening process for participants.

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There were 80 patients with CC recurrence, accounting for 9% of all participants. The proportion of participants at FIGO stage I was higher in the nonrecurrence group than the recurrence group (30.57% vs. 26.25%). The median D-dimer level was lower in the nonrecurrence group than the recurrence group (0.34 mg/L vs. 0.42 mg/L). The percentage of patients in the EG in the nonrecurrence group was lower than in the recurrence group (23.51% vs. 41.25%). More information on the characteristics of participants was exhibited in Table 1.

Association Between D-Dimer Levels and Risk of CC Recurrence

As shown in Supplementary Table 3, SCC, tumor stage, positive lymph nodes, depth of interstitial infiltration, infiltration of lymphatic vascular space, paracentric tissue infiltration, and lymphatic metastasis were confounding factors associated with the risk of recurrence of CC patients at the early stage. The **crude model suggested an increased risk of**

Table 1 Baseline characteristics of participants with early CC

	Total (n=888)	Recurrence, no (n=808)	Recurrence, yes (n=80)	Statistics	*P*
Age, years (mean ± SD)	50.35±8.94	50.34±8.94	50.46±9.02	t=−0.113	0.910
BMI, n (%)				—	0.608
Normal	521 (58.67)	468 (57.92)	53 (66.25)		
Underweight	30 (3.38)	28 (3.47)	2 (2.5)		
Overweight	276 (31.08)	255 (31.56)	21 (26.25)		
Obese	61 (6.87)	57 (7.05)	4 (5)		
Diabetes, n (%)				—	0.284
No	843 (94.93)	769 (95.17)	74 (92.5)		
Yes	45 (5.07)	39 (4.83)	6 (7.5)		
Hypertension, n (%)				χ^2=0.724	0.395
No	776 (87.39)	709 (87.75)	67 (83.75)		
Yes	112 (12.61)	99 (12.25)	13 (16.25)		
Other diseases, n (%)				χ^2=0.998	0.318
No	790 (88.96)	722 (89.36)	68 (85)		
Yes	98 (11.04)	86 (10.64)	12 (15)		
Hemoglobin, g/L (mean ± SD)	124.72±16.34	124.85±16.20	123.42±17.75	t=0.742	0.458
RBCs (10^{12}/L), median (Q_1–Q_3)	4.37 (4.05–4.62	4.37 (4.06–4.62	4.3 (3.95–4.62	W=35,200.5	0.188
WBCs, 10^9/L (mean ± SD)	6.80±2.25	6.78±2.24	6.93±2.35	t=−0.566	0.571
Platelets, 10^9/L (mean ± SD)	264.10±69.54	263.51±68.46	270±79.91	t'=−0.701	0.485
Neutrophils, 10^9/L (mean ± SD)	3.9 (3.1–5.3)	3.9 (3.1–5.3)	3.8 (3.08–5.6)	W=31,415	0.679
Lymphocytes (10^9/L), median (Q_1–Q_3)	1.9 (1.5–2.3)	1.9 (1.5–2.3)	1.8 (1.5–2.3)	W=33,885.5	0.474
Monocytes (10/L), median (Q_1–Q_3)	0.36 (0.27–0.48)	0.36 (0.27–0.48)	0.33 (0.27–0.45)	W=33,503	0.589
Eosinophils (10^9/L), median (Q_1–Q_3)	0.1 (0.05–0.2)	0.1 (0.05–0.2)	0.08 (0.04–0.18)	W=36,110	0.083
Basophils (10^9/L), median (Q_1–Q_3)	0.03 (0.02–0.06)	0.03 (0.02–0.06)	0.04 (0.02–0.06)	W=30,035	0.292
MPV, fL (mean ± SD)	10.69±1.55)	10.68±1.46)	10.77±2.23)	t'=−0.355	0.724
RDW (%), median (Q_1–Q_3)	12.7 (12.1–13.4)	12.7 (12.1–13.4)	12.55 (11.97–13.3)	W=34,771.5	0.262
ALT (U/L), median (Q_1–Q_3)	14.5 (11–21)	14.5 (11–21)	14.5 (11–19)	W=33,671.5	0.536
AST, U/L), median (Q_1–Q_3)	19 (17–23)	19 (16–23)	19 (17–22)	W=30,651.5	0.445
GGT (U/L), median (Q_1–Q_3)	18 (14–26)	18 (14–26)	19 (14–26)	W=31,536	0.720
ALP, U/L (mean ± SD)	83.31±27.08	83.39±26.96	82.49±28.41	t=0.283	0.777
LDH (U/L), median (Q_1–Q_3)	168 (148–191)	168 (147.75–191)	165.5 (151–187.25)	W=33,267.5	0.665
TBil (μmol/L), median (Q_1–Q_3)	11.3 (9–14.4)	11.3 (8.97–14.4)	11.55 (9.6–13.65)	W=31,346.5	0.657
DBil (μmol/L), median (Q_1–Q_3)	2.1 (1.6–2.6)	2.1 (1.6–2.6)	2 (1.67–2.62)	W=31,069	0.567
IBil, μmol/L (mean ± SD)	9.89±3.82	9.88±3.86	9.94±3.47	t=−0.130	0.897
Total protein, g/L (mean ± SD)	72.89±5.64	72.88±5.70	73.03±5.11	t=−0.237	0.813
Albumin, g/L (mean ± SD)	42.45±3.53	42.43±3.55	42.72±3.37	t=−0.712	0.477
Globulin, g/L (mean ± SD)	30.36±4.20	30.37±4.25	30.32±3.70	t=0.105	0.916
PT (seconds), median (Q_1–Q_3)	11.95 (11.3–12.6)	11.9 (11.3–12.5)	12.15 (11.57–12.7)	W=28,176	0.058
APTT, seconds (mean ± SD)	31.22±5.32	31.24±5.33	31.09±5.16	t=0.227	0.820
TT (seconds), median (Q_1–Q_3)	16.8 (15.8–17.6)	16.8 (15.8–17.6)	16.35 (15.5–17.2)	W=37,421	0.020

(*Continued*)

Table 1 (Continued).

	Total (n=888)	Recurrence, no (n=808)	Recurrence, yes (n=80)	Statistics	*P*
Fibrinogen, n (%)				χ^2=0.438	0.508
<4	791 (89.08)	722 (89.36)	69 (86.25)		
≥4	97 (10.92)	86 (10.64)	11 (13.75)		
SCC-Ag, n (%)				χ^2=8.796	0.003
<4	707 (79.62)	654 (80.94)	53 (66.25)		
≥4	181 (20.38)	154 (19.06)	27 (33.75)		
FIGO stage, n (%)				χ^2=0.456	0.5
I	268 (30.18)	247 (30.57)	21 (26.25)		
II	620 (69.82)	561 (69.43)	59 (73.75)		
Histology, n (%)				χ^2=5.94	0.051
Adenocarcinoma	122 (13.74)	108 (13.37)	14 (17.5)		
Others	61 (6.87)	51 (6.31)	10 (12.5)		
Squamous carcinoma	705 (79.39)	649 (80.32)	56 (70)		
Tumor size, n (%)				χ^2=1.649	0.438
<2 cm	150 (16.89)	137 (16.96)	13 (16.25)		
≥4 cm	144 (16.22)	127 (15.72)	17 (21.25)		
2–4 cm	594 (66.89)	544 (67.33)	50 (62.5)		
Tumor stage, n (%)				—	0.001
I	53 (5.97)	51 (6.31)	2 (2.5)		
II	649 (73.09)	601 (74.38)	48 (60)		
III	186 (20.95)	156 (19.31)	30 (37.5)		
Positive lymph nodes, n (%)				—	0.114
No	655 (73.76)	603 (74.63)	52 (65)		
Unknown	29 (3.27)	27 (3.34)	2 (2.5)		
Yes	204 (22.97)	178 (22.03)	26 (32.5)		
Number of lymph nodes removed (mean ± SD)	26.84±9.58	26.93±9.60	25.99±9.31	*t*=0.838	0.402
Depth of interstitial infiltration, n (%)				χ^2=10.062	0.018
Central	160 (18.02)	152 (18.81)	8 (10)		
Inside	208 (23.42)	192 (23.76)	16 (20)		
No	108 (12.16)	102 (12.62)	6 (7.5)		
Outside	412 (46.4)	362 (44.8)	50 (62.5)		
Infiltration of lymphatic vascular space, n (%)				χ^2=12.685	<0.001
No	547 (61.6)	513 (63.49)	34 (42.5)		
Yes	341 (38.4)	295 (36.51)	46 (57.5)		
Paracentric tissue infiltration, n (%)				—	0.005
No	863 (97.18)	790 (97.77)	73 (91.25)		
Yes	25 (2.82)	18 (2.23)	7 (8.75)		
Lymphatic metastasis, n (%)				—	<0.001
No	744 (83.78)	701 (86.76)	43 (53.75)		
Paraaortic metastasis	1 (0.11)	1 (0.12)	0 (0)		
Pelvic metastasis more than 5	16 (1.8)	6 (0.74)	10 (12.5)		
Pelvic metastasis no more than 5	127 (14.3)	100 (12.38)	27 (33.75)		
Positive incisal margin, n (%)				—	1
No	873 (98.31)	794 (98.27)	79 (98.75)		
Yes	15 (1.69)	14 (1.73)	1 (1.25)		
Preoperative tapering, n (%)				χ^2=0.184	0.668
No	795 (89.53)	725 (89.73)	70 (87.5)		
Yes	93 (10.47)	83 (10.27)	10 (12.5)		
Surgical method, n (%)				—	0.242
Laparoscopy	55 (6.19)	53 (6.56)	2 (2.5)		
Laparotomy	537 (60.47)	483 (59.78)	54 (67.5)		
Laparotomy + laparoscopy	296 (33.33)	272 (33.66)	24 (30)		
Surgery length (hours), median (Q_1–Q_3)	3.83 (3.28–4.58)	3.83 (3.28–4.58)	3.96 (3.4–4.52)	*W*=30,752	0.474

(*Continued*)

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Table 1 (Continued).

	Total (n=888)	Recurrence, no (n=808)	Recurrence, yes (n=80)	Statistics	*P*
Sentinel lymph-node biopsy, n (%)				—	0.574
No	879 (98.99)	800 (99.01)	79 (98.75)		
Yes	9 (1.01)	8 (0.99)	1 (1.25)		
D-dimer (mg/L), median (Q_1–Q_3)	0.34 (0.22–0.5)	0.34 (0.22–0.48)	0.42 (0.25–0.68)	*W*=26,677.5	0.010
D-dimer, n (%)				χ^2=11.250	0.001
NG	665 (74.89)	618 (76.49)	47 (58.75)		
EG	223 (25.11)	190 (23.51)	33 (41.25)		

Abbreviations: Q_1, first quartile; Q_3, third quartile; *t*, Student's *t*; *t'*, Satterthwaite's *t*; *W*, Wilcoxon's rank-sum test; BMI, body mass index; RBCs, red blood cells; WBCs, white blood cells; MPV, mean platelet volume; RDW, RBC distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; TBil, total bilirubin; DBil, direct bilirubin; IBil, indirect bilirubin; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; SCC-Ag, squamous cell carcinoma antigen; FIGO, International Federation of Gynecology and Obstetrics; NG, normal group; EG, elevated group.

recurrence inthe EG compared to the NG. We found that the risk of recurrence was elevated in patients in the EG, with an adjusted OR of 2.16 (95% CI 1.28–3.62) (Table 2).

In patients with cervical squamous cell carcinoma, infiltration of lymphatic vascular space, paracentric tissue infiltration, and lymphatic metastasis were covariates related to the risk of recurrence (Supplementary Table 4). The risk of recurrence was elevated in the EG in patients with cervical squamous cell carcinoma undergoing surgery in the adjusted model (OR 3.58, 95% CI 1.02–12.89; Table 2). As for cervical adenocarcinoma patients, an increased risk of recurrence was identified in those in the EG (OR 1.87, 95% CI 1.01–3.48; Table 2) after adjusting for covariates, including SCC-Ag, positive lymph node, depth of interstitial infiltration, infiltration of lymphatic vascular space, paracentric tissue infiltration, and lymphatic metastasis (Supplementary Table 5). RCS curves indicated that the risk of recurrence increased with the elevation in D-dimer levels in the whole population of CC, cervical squamous cell carcinoma, and cervical adenocarcinoma patients (Figure 2).

Subgroup Analysis of Association Between D-Dimer Levels and Risk of CC Recurrence

In early-CC patients <55 years, D-dimer levels in the EG were associated with increased risk of recurrence (OR 2.16, 95% CI 1.10–4.19) and were correlated with elevated risk of recurrence in CC patients with tumor size ≥4 cm (OR 4.67,

Table 2 Association between D-dimer levels and risk of CC recurrence

		Model 1		Model 2	
	n (%)	OR (95% CI)	*P*	OR (95% CI)	*P*
Total population					
NG	665 (74.89)	Ref		Ref	
EG	223 (25.11)	2.28 (1.41–3.66)	0.001	2.16 (1.28–3.62)	0.004
Cervical squamous cell carcinoma					
NG	91 (74.59)	Ref		Ref	
EG	31 (25.41)	4.93 (1.56–16.37)	0.007	3.58 (1.02–12.89)	0.045
Cervical adenocarcinoma					
NG	530 (75.18)	Ref		Ref	
EG	175 (24.82)	1.93 (1.09–3.41)	0.024	1.87 (1.01–3.48)	0.048

Note: Model 1: univariablivariate model without adjusting any variable. Model 2: Mutivariable multivariate model adjusted for SCC-Ag, tumor stage, positive lymph nodes, depth of interstitial infiltration, infiltration of lymphatic vascular space, pracentric tissue infiltration, and lymphatic metastasis in total population; infiltration of lymphatic vascular space, paracentric tissue infiltration, and lymphatic metastasis in cervical squamous cell carcinoma population; SCC-Ag, positive lymph node, depth of interstitial infiltration, infiltration of lymphatic vascular space, paracentric tissue infiltration and lymphatic metastasis in total population and cervical adenocarcinoma population.

Abbreviations: OR, Odds ratio; CI, Confidence intervals; Ref, reference;

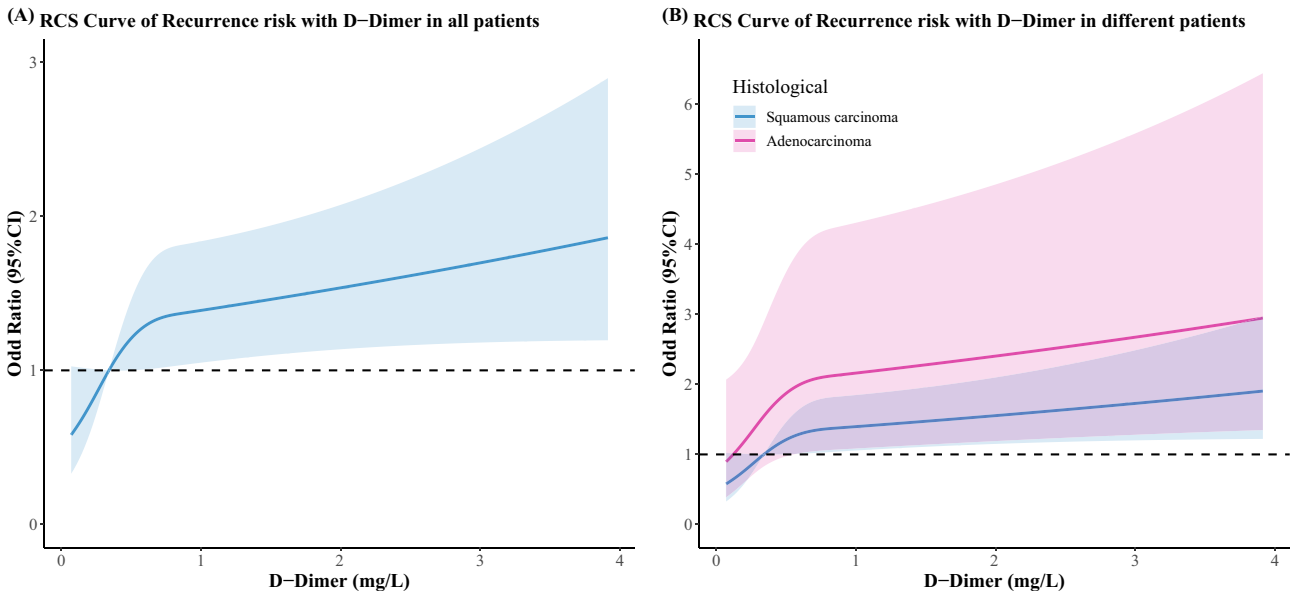

Figure 2 RCS curves showing the association between D-dimer levels and ORs of recurrence in CC patients. (**A**) RCS curve of recurrence risk vs. D-dimer in all patients; (**B**) RCS curve of recurrence risk vs. D-dimer in patients with squamous cell carcinoma or adenocarcinoma.

95% CI 1.14–21.82). In CC patients with outside interstitial infiltration, the risk of recurrence was higher in the EG than the NG (OR 2.12, 95% CI 1.08–4.15). We also observed an elevated risk of recurrence in CC patients receiving laparotomy (OR 2.70, 95% CI 1.43–3.55; Figure 3).

Discussion

The current study evaluated the association between D-dimer level and the risk of recurrence in CC patients at the early stage. The results showed that early-stage CC patients with high levels of D-dimer receiving surgical treatment had a increased risk of recurrence. The risk of recurrence in patients with cervical squamous cell carcinoma or cervical adenocarcinoma undergoing surgery was elevated in those with high D-dimer levels. RCS curves indicated that the risk of recurrence increased with the elevation in D-dimer levels in the whole population of CC, cervical squamous cell carcinoma, and cervical adenocarcinoma patients. The findings might provide a reference for the management of early-stage CC patients.

A growing body of research has provided evidence that D-dimer levels are associated with the prognosis of cancers. A systematic review and meta-analysis indicated that high plasma D-dimer levels led to shorter survival than low plasma D-dimer levels, which might help predict the prognosis in patients with lung cancer.[9] The plasma D-dimer level in ovarian cancer patients has been reported to serve as a predictive indicator of disease progression and the risk of venous thromboembolism.[14] An association between D-dimer levels and recurrent stroke in cancer-related hypercoagulability-related stroke patients has been observed following anticoagulant therapy. Patients with a stable elevation in D-dimer levels after receiving anticoagulant therapy exhibited a significantly increased risk of recurrent stroke in another study.[15] In other research, elevated D-dimer levels provided significant prognostic information and were associated with the recurrence of venous thromboembolism, serving as an indicator of biologically more aggressive cancer types and advanced stages of cancer.[16] As for patients with CC, preoperative D-dimer has been reported to be the most effective predictor of prognosis.[17] High pretreatment plasma levels of D-dimer have been identified to be an independent prognostic index for CC.[18] Another systematic review and meta-analysis revealed that high plasma D-dimer levels predict poor prognosis in gynecological tumors, including CC, in the East Asia area.[19] In addition, elevation in postoperative D-dimer levels has an impact on tumor recurrence and long-term survival in patients with gastric cancer who undergo gastrectomy.[20] In our study, high levels of D-dimer were associated with increased risk of recurrence in early-CC patients receiving surgery.

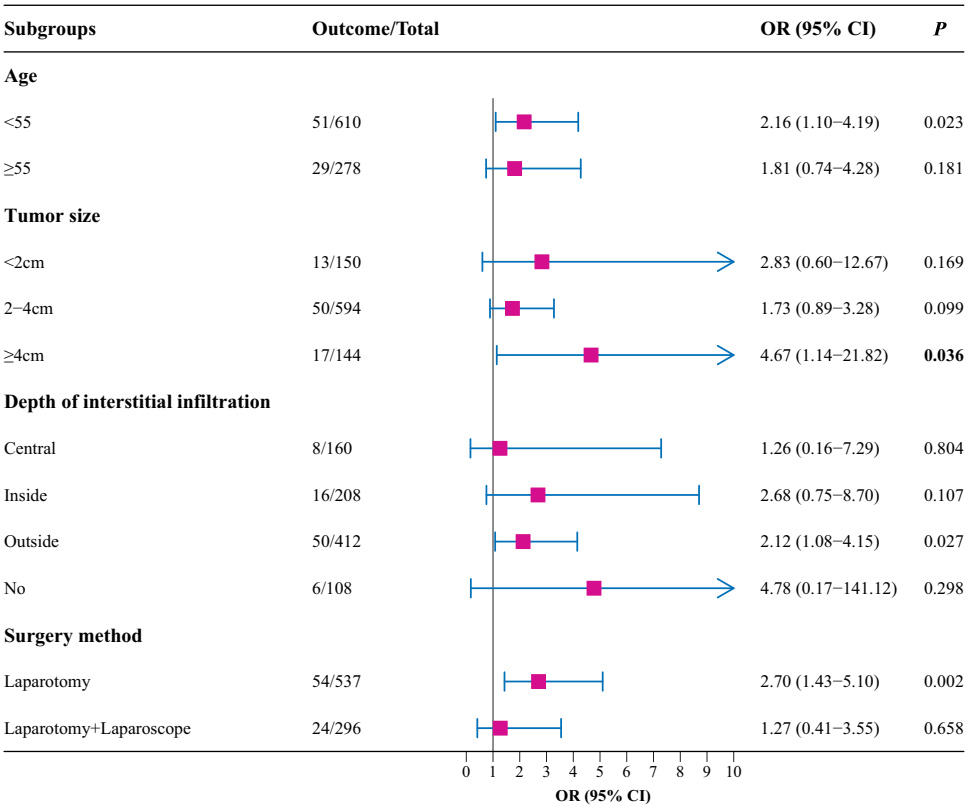

Figure 3 Subgroup analysis of association between D-dimer levels and risk of CC recurrence.

The possible mechanisms might be that activation of the hemostatic system plays a pivotal role in tumor development, dissemination, and metastasis.[21] Plasminogen activators generate plasmin, which has been implicated in both tumor invasion and the intravasation of neoplastic cells.[22,23] D-dimer levels are associated with tumor metastasis.[24,25] The activated coagulation system, which might be aggravated by both the surgical procedure and the postoperative surgical stress, might exacerbate micrometastases in patients with CC.[26] Tumor cells, fibrin, and platelets are known to form complexes that provide support for circulating tumor cells in the bloodstream by affording protection against the shear forces of blood flow and natural killer cell–mediated elimination.[27] These complexes also facilitate adhesion to the vessel wall and extravasation of metastases into the tissue. Moreover, activated platelets secrete growth factors, such as VEGF, TGFβ, and PDGF, which exert influences on tumor angiogenesis and proliferation.[17] Postoperative hypercoagulation status may also potentiate these mechanisms, and D-dimer, a stable end product of the coagulation cascade, could serve as a biomarker for recurrence in patients with CC. These potential mechanisms require exploration in more studies.

This study evaluated the relationship between plasma D-dimer levels and the risk of recurrence after surgical treatment in patients with early CC, which might offer a novel insight in the management of prognosis of early CC patients. For those with high D-dimer levels, frequent monitoring and early interventions should be provided. Recent evidence showed significant advancements, including the introduction of immunotherapy and targeted therapies in the outcomes of recurrent CC. New therapies, such as novel pharmacotherapy and combination strategies, are required to improve the outcome of CC patients.[28] Primary and secondary prevention and adequate screening are the fundamental goals for reducing the burden of CC.[29]

There were some limitations in our study. Firstly, this was a single-center retrospective study, and selection bias might exist. Secondly, only the association between plasma D-dimer levels and recurrence risk in patients with early CC could be identified, and the causal link between D-dimer levels and recurrence risk is unknown. Thirdly, the sample of patients with cervical adenocarcinoma was small, and the results require validation in future studies.

Conclusion

The association between D-dimer levels and the risk of recurrence in early-stage CC patients after surgery was analyzed in the present study. The results showed that the recurrence risk of early-stage CC patients receiving surgical treatment was increased in those with high levels of D-dimer. The causal association between D-dimer levels and the risk of recurrence in CC patients needs validation in future studies.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board of the Clinical Oncology School of Fujian Medical University Fujian Cancer Hospital. The need for written informed consent was waived by the board due to the retrospective nature of the study. All patient data were kept confidential and all methods were performed in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether is in the conception, study design, execution, acquisition of data, analysis, interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

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