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Prognostic significance of lymphovascular space invasion in patients with endometrioid endometrial cancer: a retrospective study from a single center

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ABSTRACT

Objective: This study aims to analyze factors associated with lymphovascular space invasion (LVSI) and evaluate the prognostic significance of LVSI in Chinese endometrioid endometrial cancer (EEC) patients.

Methods: Five-hundred eighty-four EEC patients undergoing surgery in our center from 2006 to 2016 were selected for analysis. Univariate analysis and multivariate logistic regression were used to examine relevant factors of LVSI. To evaluate the prognostic role of LVSI, survival analyses were conducted. In survival analyses, both multivariate Cox regression and propensity score matching were used to control the confounders.

Results: The incidence of LVSI was 12.16% (71/584). Diabetes history ($p=0.021$), lymph node metastasis ($p=0.005$), deep myometrial invasion ($p<0.001$) and negative PR expression ($p=0.007$) were independently associated with LVSI. Both Kaplan-Meier method and univariate Cox regressions showed LVSI negative and positive cases had similar tumor-specific survival (TSS) and disease-free survival (DFS). After adjusting for the influence of adjuvant therapy and other clinicopathological factors with multivariate Cox regressions, LVSI still could not bring additional survival risk to the patients ($p=0.280$ and $p=0.650$ for TSS and DFS, respectively). This result was verified by Kaplan-Meier survival analyses after propensity score matching ($p=0.234$ and $p=0.765$ for TSS and DFS, respectively).

Conclusion: LVSI does not significantly compromise the survival outcome of Chinese EEC patients.

Keywords: Endometrial Neoplasms; Lymphovascular Space Invasion; Recurrence; Survival

INTRODUCTION

Endometrial cancer is one of the most common malignant gynecological neoplasms in the Western world. According to the estimation of the American Cancer Society, there were 63,230 new endometrial cancer cases and 11,350 deaths in the US last year [1]. In China, the morbidity of endometrial cancer ranks second among all gynecological malignancies

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

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and is still increasing [2]. Generally, endometrial cancer patients have a relatively favorable outcome. However, the survival of patients with metastatic/recurrent disease is usually poor [3]. Researchers have found several clinicopathological factors with predictive value for tumor recurrence and worse survival, such as older age, deep myometrial invasion, grade 3 disease and lymphovascular space invasion (LVSI) [4].

Actually, LVSI has long been considered as a potential adverse prognostic factor in endometrial cancer. Researchers found that LVSI positive patients showed a higher rate of lymph node metastasis (LNM), were more likely to have local or distal relapse and usually had shorter overall survival (OS) [5-12]. The American National Comprehensive Cancer Network (NCCN) guideline, the American College of Obstetricians and Gynecologists/Society of Gynecologic Oncology (ACOG/SGO) guideline and the European Society for Medical Oncology, the European Society of Gynecological Oncology, the European Society of Radiotherapy and Oncology (ESMO-ESGO-ESTRO) guideline for endometrial cancer all consider LVSI as a risk factor and recommend LVSI positive early stage patients to receive adjuvant therapy after surgery [13-15]. Nevertheless, in recent years, there are some studies from different countries showing negative results regarding the prognostic role of LVSI [16-20]. Then will there be a potential benefit of omitting adjuvant treatment in LVSI positive patients without other risk factors? In China, relevant data especially from a large population are still in shortage. Besides, a recent survey among gynecological oncologists revealed that LVSI is still a controversial issue as to doctors' attitude toward it and its clinical management [21]. Taking all these into account, it is necessary to reconsider the significance of this pathological phenomenon in Chinese circumstances.

This study aims to evaluate the relevant clinicopathological factors of LVSI and its survival influence on Chinese endometrioid endometrial cancer (EEC) patients.

MATERIALS AND METHODS

1. Study population and data collection

All 783 patients diagnosed as endometrial cancer and underwent surgery in Peking University People's Hospital between January 2006 and December 2016 were retrospectively reviewed. We excluded patients treated for recurrent disease (n=13), with a history of other malignancies (n=5), having already received treatment before surgeries (n=21), or only undergoing hysteroscopic examinations (n=83). Patients with non-endometrioid pathological types (n=77) were also excluded. Finally, 584 pathologically confirmed EECs were selected for further analysis.

For all eligible patients, total hysterectomy, bilateral salpingo-oophorectomy, selective bilateral pelvic and para-aortic lymphadenectomy and pelvic washings were performed by gynecological oncologists. Data about each patients' baseline information, pathological results and post-surgery adjuvant therapy use were collected. All pathological information was extracted from the original pathology reports. Pathology slides were reviewed by two independent gynecological pathologists, and controversial cases were submitted to the expert meeting for a final decision. The staging of all cases was based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system [22]. Patients treated before 2009 were restaged according to the clinicopathological information. Histological classification and tumor grade were determined according to the World Health

Organization (WHO) classification system and FIGO criteria, respectively [23]. LVSI was defined as the presence of adenocarcinoma, of any extent, in endothelium-lined channels of uterine specimens at the time of surgery [24]. A positive immunohistochemical (IHC) result for estrogen receptor (ER), progesterone receptor (PR) or p53 was defined as over 10% of tumor cells being moderately or strongly stained in one slide, and Ki67 index was determined according to the percentage of positively stained tumor cells. The study was approved by the Institutional Review Boards of Peking University People's Hospital (2016PHB054-01).

2. Follow-up

All patients were followed up after surgery through outpatient visits or phone calls. The latter was used in those routinely examined in local hospitals, and information gathered included patients' symptoms, serum carbohydrate antigen (CA) 125, CA199, results of pelvic ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI), etc. Recurrences and deaths of any cause during follow-up were recorded. In telephone follow-up, upon any abnormal findings, the patients were required to take further examinations in our center, and the diagnosis of recurrence was made accordingly. The reasons for termination of follow-up included: deaths due to endometrial cancer or any other reasons; loss of contact; reaching the final follow-up date (July 10, 2017). The median follow-up time for all 584 patients was 53.38 months (ranging from 2.50 to 109.60 months).

3. Definitions

Tumor-specific survival (TSS) was calculated from the surgery date to when death due to endometrial cancer or related treatment occurred. Disease-free survival (DFS) was defined as the interval from the surgery date to when a relapse of endometrial cancer was confirmed. Patients without a recorded event were censored at their last follow-up in survival analysis.

4. Statistical analysis

Multiple clinicopathological factors were compared between LVSI negative and LVSI positive patients. Student t-test and χ^2 test were used for comparing continuous and categorical variables, respectively. The tendency of association between grade and LVSI was analyzed using linear-by-linear association. Stepwise logistic regression (method: forward: conditional; entry criteria for variables: $p < 0.05$) was conducted to find factors independently associated with LVSI. To find potential prognostic indicators, Kaplan-Meier survival analyses (log-rank tests) and univariate Cox regressions were performed. To further analyze the survival influence of LVSI, multivariate Cox regression and propensity score matching were used to control confounders. In multivariate Cox regressions, besides LVSI, factors with $p < 0.05$ in univariate analyses were included. For all Cox regression models, the proportional hazard hypothesis was examined with time-dependent covariates. In propensity score matching, independent predictors of LVSI and adjuvant therapy use were matched, with match ratio being 1:1 and caliper width being 0.02. After matching, 2 cohorts with comparable baseline characteristics were established for further survival analyses (**Fig. 1**). Finally, in order to eliminate multicollinearity among variables and select key survival predictors for EEC patients, stepwise Cox regressions were conducted (included variables: factors with $p < 0.05$ in univariate Cox regressions; method: forward: conditional; entry criteria for variables: $p < 0.05$). All statistical analyses were finished using Statistics Package for the Social Sciences (SPSS) software (SPSS version 22.0; IBM Corporation, Armonk, NY, USA). The p-values less than 0.05 were considered statistically significant.

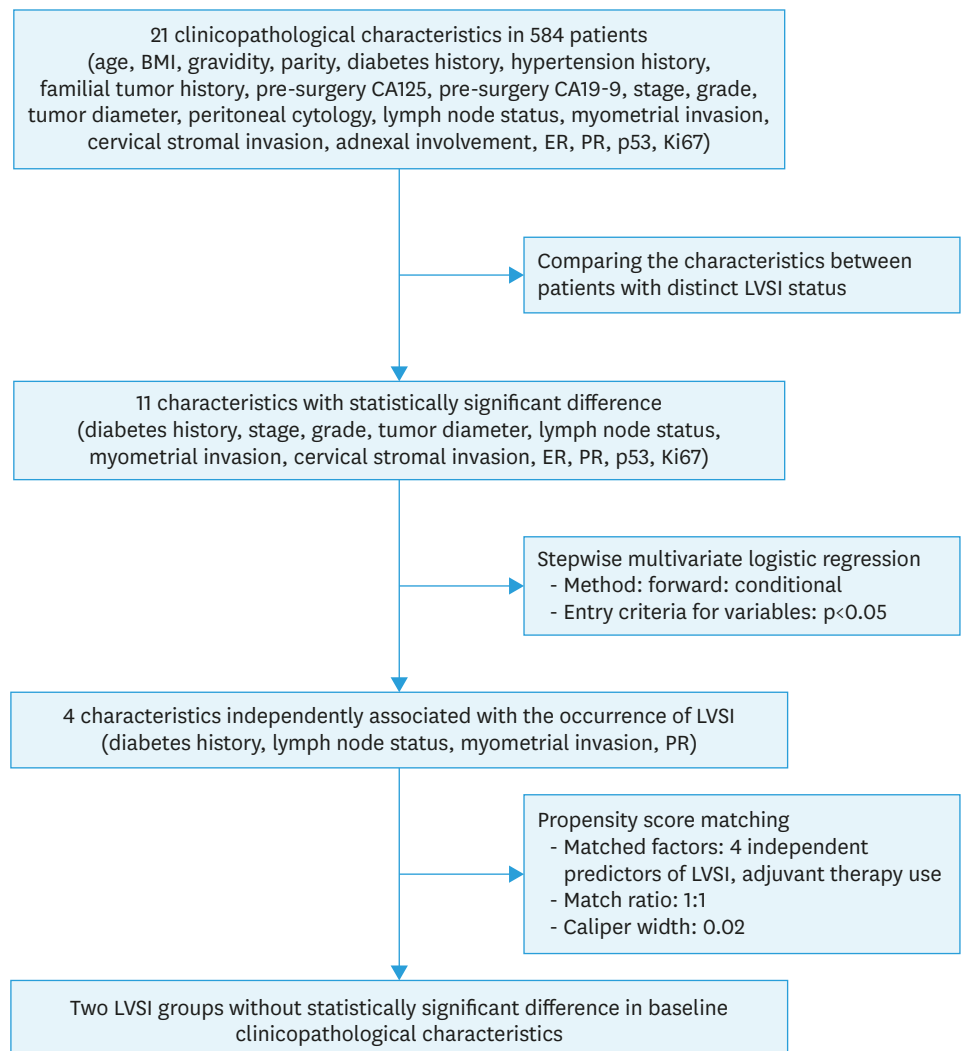


Fig. 1. Flow diagram for propensity score matching. BMI, body mass index; CA, carbohydrate antigen; ER, estrogen receptor; LVSI, lymphovascular space invasion; PR, progesterone receptor.

RESULTS

The 584 eligible patients came from 20 provinces of China. Among all of them, 513 (87.84%) were negative for LVSI and 71 (12.16%) were LVSI positive. The mean age of all patients was 55.20. There was no significant age difference between the 2 groups ($p=0.200$). Body mass index (BMI), gravidity, parity, hypertension history, family history of tumors, and the level of pre-surgery tumor markers were also similar between patients with distinct LVSI status. Diabetes mellitus was more common in LVSI positive patients ($p=0.001$). Most of the patients were in early stage (FIGO stage I–II, $n=521$, 89.21%). FIGO stage was significantly higher in LVSI positive group ($p<0.001$; **Table 1**).

Multiple pathological factors were also analyzed. LVSI positive tumors showed higher grade ($p<0.001$), larger size ($p<0.001$) and a different IHC pattern, including negative ER ($p=0.031$) and PR ($p<0.001$) expression, positive p53 expression ($p=0.021$) and higher Ki67 index

Table 1. Clinicopathological characteristics in 584 patients by LVSI status

Characteristic	LVSI negative (n=513)	LVSI positive (n=71)	p value
Age	55.03±9.51	56.42±8.39	0.200
BMI (kg/m ²)	26.41±4.52	25.70±3.68	0.205
Gravidity	2.48±1.42	2.37±1.52	0.568
Parity	1.41±0.98	1.40±0.92	0.927
Diabetes history			0.001
No	410 (79.92)	44 (61.97)	
Yes	103 (20.08)	27 (38.03)	
Hypertension history			0.554
No	299 (58.28)	44 (61.97)	
Yes	214 (41.72)	27 (38.03)	
Familial tumor history			0.916
No	431 (84.02)	60 (84.51)	
Yes	82 (15.98)	11 (15.49)	
Pre-surgery CA125 (U/mL)	37.22±77.96	53.82±111.61	0.132
Pre-surgery CA19-9 (U/mL)	35.50±84.33	35.05±65.52	0.970
Stage			<0.001
Early (I–II)	469 (91.42)	52 (73.24)	
Advanced (III–IV)	44 (8.58)	19 (26.76%)	
Grade			<0.001
1	208 (40.55)	11 (15.49)	
2	250 (48.73)	38 (53.52)	
3	55 (10.72)	22 (30.99)	
Tumor diameter (cm)	2.69±2.57	3.84±2.44	<0.001
Peritoneal cytology			1.000
Negative	380 (94.53)	50 (94.34)	
Positive	22 (5.47)	3 (5.66)	
Lymph node status			<0.001
Negative	412 (94.28)	50 (78.13)	
Positive	25 (5.72)	14 (21.88)	
Myometrial invasion			<0.001
<50%	417 (81.29)	37 (52.11)	
≥50%	96 (18.71)	34 (47.89)	
Cervical stromal invasion			0.009
No	474 (92.40)	59 (83.10)	
Yes	39 (7.60)	12 (16.90)	
Adnexal involvement			0.744
No	499 (97.27)	68 (95.77)	
Yes	14 (2.73)	3 (4.23)	
Surgical specimen IHC			
ER			0.031
Negative	18 (3.68)	7 (10.29)	
Positive	471 (96.32)	61 (89.71)	
PR			<0.001
Negative	14 (2.86)	9 (13.24)	
Positive	475 (97.14)	59 (86.76)	
P53			0.021
Negative	217 (46.27)	21 (31.34)	
Positive	252 (53.73)	46 (68.66)	
Ki67 (%)	33.24±20.90	41.89±17.96	0.002
Adjuvant therapy use			<0.001
No	209 (50.36)	14 (20.00)	
Yes	206 (49.64)	56 (80.00)	

The values are presented as mean±standard deviation, or number (%), unless otherwise indicated. Bold-font values indicate p values less than 0.05, which is considered statistically significant.

BMI, body mass index; CA, carbohydrate antigen; ER, estrogen receptor; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; PR, progesterone receptor.

($p=0.002$), indicating worse differentiation and more active proliferation. LNM ($p<0.001$), deep myometrial invasion (defined as $\geq 50\%$ myometrium involved, $p<0.001$) and cervical stromal invasion ($p=0.009$) were all more common in LVSI positive cases. But there was no statistically significant difference in peritoneal cytology findings ($p=1.000$) and adnexal involvement ($p=0.744$; **Table 1**).

All factors showing statistical significance above were included into the multivariate logistic regression. After selecting the variables with stepwise regression, only diabetes history ($p=0.021$), LNM ($p=0.005$), deep myometrial invasion ($p<0.001$) and negative PR expression ($p=0.007$) were independently associated with the occurrence of LVSI.

Then the survival influence of multiple factors was analyzed. In Kaplan-Meier survival analyses, age ≥ 65 ($p=0.008$ and $p=0.024$ for TSS and DFS), advanced stage (FIGO stage III–IV, $p<0.001$ for TSS and DFS), high grade (grade 3, $p<0.001$ for TSS and DFS), large tumor size (≥ 2 cm in diameter, $p=0.001$ for TSS, $p<0.001$ for DFS), positive peritoneal cytology ($p<0.001$ for TSS and DFS), LNM ($p<0.001$ for TSS and DFS), deep myometrial invasion ($p=0.003$ for DFS) and adnexal involvement ($p<0.001$ for TSS and DFS) all effected patients' survival in varying degrees. Endometrial cancer with negative ER ($p<0.001$ for TSS and DFS) and PR ($p=0.002$ and $p=0.005$ for TSS and DFS, respectively) expression had poorer prognosis. Univariate Cox regressions showed similar results (**Table 2**). However, in both methods, positive LVSI did not compromise the survival outcomes of EEC patients significantly, especially in terms of TSS (in Kaplan-Meier analyses, $p=0.786$ and $p=0.072$ for TSS and DFS; in univariate Cox regressions, $p=0.786$ and $p=0.079$ for TSS and DFS, respectively) (**Table 2, Fig. 2A and B**).

Table 2. Cox regression analysis for prognostic factors of TSS and DFS rate

Characteristic	Univariate analysis				Multivariate analysis			
	TSS		DFS		TSS		DFS	
	HR (95% CI)	p value	HR (95% CI)	p value	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Advanced age (≥ 65)	3.332 (1.302–8.528)	0.012	2.372 (1.093–5.148)	0.029	4.616 (1.238–17.205)	0.023	3.836 (1.388–10.603)	0.010
High BMI (≥ 28 kg/m ²)	1.802 (0.711–4.566)	0.215	1.866 (0.920–3.786)	0.084	-	-	-	-
No pregnancy	1.721 (0.395–7.493)	0.470	1.454 (0.442–4.784)	0.538	-	-	-	-
No labor	1.493 (0.426–5.230)	0.531	1.137 (0.395–3.270)	0.812	-	-	-	-
Positive diabetes history	1.286 (0.462–3.579)	0.630	1.425 (0.659–3.083)	0.369	-	-	-	-
Positive hypertension history	1.938 (0.775–4.842)	0.157	1.620 (0.807–3.253)	0.175	-	-	-	-
Positive familial tumor history	2.043 (0.770–5.420)	0.151	1.099 (0.451–2.680)	0.836	-	-	-	-
Elevated CA125 (≥ 35 U/mL)	2.368 (0.882–6.360)	0.087	1.946 (0.912–4.155)	0.085	-	-	-	-
Elevated CA19-9 (≥ 37 U/mL)	1.278 (0.346–4.721)	0.713	1.375 (0.542–3.487)	0.503	-	-	-	-
Advanced stage (stage III–IV)	11.505 (4.586–28.865)	<0.001	6.994 (3.456–14.153)	<0.001	2.725 (0.242–30.709)	0.417	1.987 (0.349–11.317)	0.439
High grade (grade 3)	7.123 (2.875–17.648)	<0.001	6.000 (2.985–12.058)	<0.001	3.145 (0.909–10.881)	0.070	5.426 (2.029–14.509)	0.001
Large tumor (diameter ≥ 2 cm)	13.327 (1.778–99.892)	0.012	7.043 (2.144–23.129)	0.001	1.197 $\times 10^5$ (4.261 $\times 10^{-158}$ –3.362 $\times 10^{167}$)	0.951	6.786 (0.858–53.702)	0.070
LVSI	1.227 (0.281–5.356)	0.786	2.225 (0.910–5.439)	0.079	0.287 (0.030–2.765)	0.280	0.738 (0.198–2.742)	0.650
Positive peritoneal cytology	10.211 (3.481–29.955)	<0.001	6.690 (2.650–16.884)	<0.001	7.493 (1.919–29.261)	0.004	6.422 (2.034–20.274)	0.002
LNM	9.870 (3.887–25.058)	<0.001	6.241 (2.936–13.269)	<0.001	1.471 (0.156–13.885)	0.736	2.035 (0.410–10.097)	0.385
Deep myometrial invasion	2.135 (0.828–5.509)	0.117	2.825 (1.393–5.732)	0.004	-	-	0.439 (0.155–1.247)	0.122
Cervical stromal invasion	1.121 (0.257–4.885)	0.879	1.388 (0.485–3.970)	0.541	-	-	-	-
Adnexal involvement	8.816 (2.543–30.557)	0.001	8.214 (3.145–21.453)	<0.001	1.438 (0.148–14.004)	0.754	2.342 (0.536–10.231)	0.258
Negative ER	7.031 (2.311–21.397)	0.001	4.713 (1.808–12.285)	0.002	2.531 (0.340–18.819)	0.364	1.491 (0.244–9.099)	0.665
Negative PR	5.585 (1.609–19.389)	0.007	4.000 (1.397–11.455)	0.010	1.164 (0.063–21.464)	0.919	0.669 (0.053–8.425)	0.756
Positive P53	1.487 (0.558–3.966)	0.428	1.609 (0.757–3.419)	0.216	-	-	-	-
High Ki67 ($\geq 40\%$)	1.703 (0.590–4.910)	0.325	2.088 (0.945–4.611)	0.069	-	-	-	-
Adjuvant therapy use	5.743 (1.311–25.159)	0.020	3.800 (1.444–9.999)	0.007	1.074 (0.201–5.753)	0.933	1.090 (0.328–3.623)	0.888

Bold-font values indicate p values less than 0.05, which is considered statistically significant.

BMI, body mass index; CA, carbohydrate antigen; CI, confidence interval; DFS, disease-free survival; ER, estrogen receptor; HR, hazard ratio; LNM, lymph node metastasis; LVSI, lymphovascular space invasion; PR, progesterone receptor; TSS, tumor-specific survival.

The prognostic effect of LVSI was further verified. After adjusting for the effect of adjuvant therapy and other adverse prognostic factors with multivariate Cox regression, LVSI status still could not predict patients' TSS ($p=0.280$) or DFS ($p=0.650$) (**Table 2**). Besides, based on two cohorts without significant difference in clinicopathological characteristics after propensity score matching (**Table 3**), Kaplan-Meier analyses showed similar survival time in LVSI positive and negative patients ($p=0.234$ and $p=0.765$ for TSS and DFS) (**Fig. 2C and D**).

Multivariate models for predicting patients' survival were established. In stepwise Cox regression, advanced age (hazard ratio [HR]=4.492, 95% confidence interval [CI]=1.320–15.294, $p=0.016$ for TSS; HR=3.267, 95% CI=1.252–8.528, $p=0.016$ for DFS), high grade (HR=4.547, 95% CI=1.453–14.225, $p=0.009$ for TSS; HR=5.178, 95% CI=2.131–12.581, $p<0.001$ for DFS), positive peritoneal cytology (HR=10.982, 95% CI=2.948–40.907, $p<0.001$ for TSS; HR=7.570, 95% CI=2.607–21.979, $p<0.001$ for DFS) and advanced stage (HR=4.446, 95% CI=1.456–13.576, $p=0.009$ for TSS; HR=4.110, 95% CI=1.739–9.713, $p=0.001$ for DFS) were shown to be independent predictors for both shorter TSS and shorter DFS (**Table 4**).

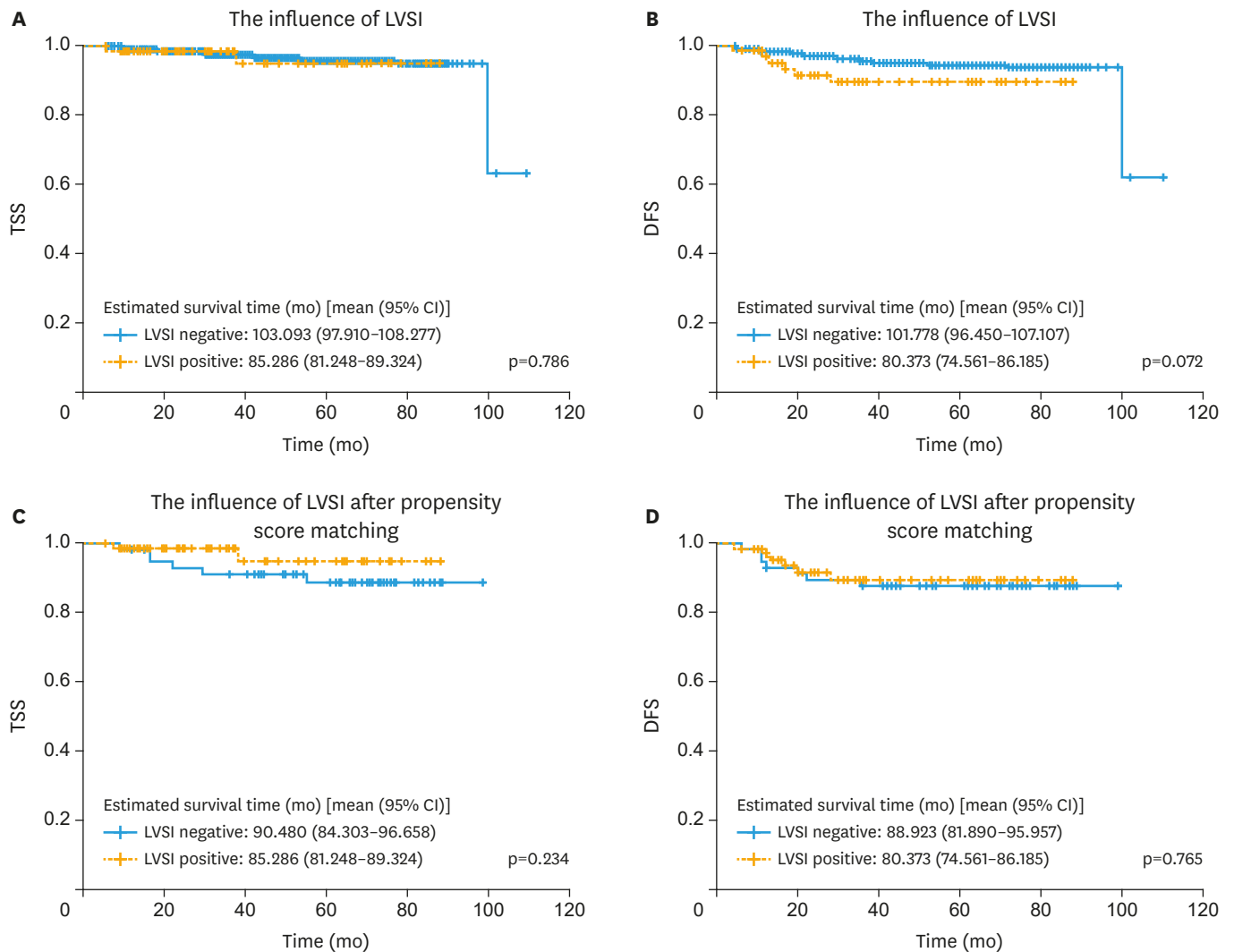


Fig. 2. The influence of LVSI on patients' survival. (A, B) Kaplan-Meier survival curves for TSS and DFS by LVSI. (C, D) Kaplan-Meier curves for TSS and DFS by LVSI in patients after propensity score matching. CI, confidence interval; DFS, disease-free survival; LVSI, lymphovascular space invasion; TSS, tumor-specific survival.

Table 3. Clinicopathological characteristics by LVSI status after propensity score matching

Characteristic	LVSI negative (n=58)	LVSI positive (n=71)	p value
Age	58.55±9.82	56.42±8.39	0.187
BMI (kg/m ²)	25.97±4.32	25.70±3.68	0.703
Gravidity	2.57±1.61	2.37±1.52	0.477
Parity	1.59±1.21	1.40±0.92	0.327
Diabetes history			0.677
No	38 (65.52)	44 (61.97)	
Yes	20 (34.48)	27 (38.03)	
Hypertension history			0.172
No	29 (50.00)	44 (61.97)	
Yes	29 (50.00)	27 (38.03)	
Familial tumor history			0.144
No	43 (74.14)	60 (84.51)	
Yes	15 (25.86)	11 (15.49)	
Pre-surgery CA125 (U/mL)	59.18±69.93	53.82±111.61	0.770
Pre-surgery CA19-9 (U/mL)	51.63±50.57	35.05±65.52	0.193
Stage			0.593
Early (I–II)	40 (68.97)	52 (73.24)	
Advanced (III–IV)	18 (31.03)	19 (26.76)	
Grade			0.490
1	14 (24.14)	11 (15.49)	
2	26 (44.83)	38 (53.52)	
3	18 (31.03)	22 (30.99)	
Tumor diameter (cm)	4.67±3.36	3.84±2.44	0.117
Peritoneal cytology			0.303
Negative	45 (86.54)	50 (94.34)	
Positive	7 (13.46)	3 (5.66)	
Lymph node status			0.943
Negative	45 (77.59)	50 (78.13)	
Positive	13 (22.41)	14 (21.88)	
Myometrial invasion			0.530
<50%	27 (46.55)	37 (52.11)	
≥50%	31 (53.45)	34 (47.89)	
Cervical stromal invasion			0.308
No	44 (75.86)	59 (83.10)	
Yes	14 (24.14)	12 (16.90)	
Adnexal involvement			1.000
No	55 (94.83)	68 (95.77)	
Yes	3 (5.17)	3 (4.23)	
Surgical specimen IHC			
ER			0.546
Negative	8 (13.79)	7 (10.29)	
Positive	50 (86.21)	61 (89.71)	
PR			0.411
Negative	5 (8.62)	9 (13.24)	
Positive	53 (91.38)	59 (86.76)	
P53			0.603
Negative	19 (35.85)	21 (31.34)	
Positive	34 (64.15)	46 (68.66)	
Ki67 (%)	36.82±23.97	41.89±17.96	0.241
Adjuvant therapy use			0.691
No	10 (17.24)	14 (20.00)	
Yes	48 (82.76)	56 (80.00)	

The values are presented as mean±standard deviation, or number (%), unless otherwise indicated.

BMI, body mass index; CA, carbohydrate antigen; ER, estrogen receptor; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; PR, progesterone receptor.

Table 4. Stepwise Cox regression models for prediction of patients' survival

Characteristic	TSS		DFS	
	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Advanced age (>65)	4.492 (1.320–15.294)	0.016	3.267 (1.252–8.528)	0.016
High grade (grade 3)	4.547 (1.453–14.225)	0.009	5.178 (2.131–12.581)	<0.001
Positive peritoneal cytology	10.982 (2.948–40.907)	<0.001	7.570 (2.607–21.979)	<0.001
Advanced stage (stage III–IV)	4.446 (1.456–13.576)	0.009	4.110 (1.739–9.713)	0.001

Bold-font values indicate p values less than 0.05, which is considered statistically significant.
 DFS, disease-free survival; CI, confidence interval; HR, hazard ratio; TSS, tumor-specific survival.

DISCUSSION

According to literature review of our group, this is the first study analyzing relevant factors and prognostic significance of LVSI in Chinese EEC patients. We found that even though the occurrence of LVSI is accompanied by several adverse prognostic factors, it by itself would not compromise patients' survival (measured by TSS and DFS) significantly. Surprisingly, this finding disagrees with most Western-population-based research results [5-12]. In addition, according to our models, besides stage, patients' age, tumor grade and peritoneal cytology should also be taken into account when considering the risk of recurrence and shorter survival.

Actually, the phenomenon of LVSI has been recognized in endometrial cancer since nearly 40 years ago [25]. A lot of researches have been performed to demonstrate its clinical significance, especially in recent years. It is now generally agreed that there is a much higher risk of LNM in LVSI positive patients. In our sample, the incidence of LNM in LVSI positive cases was 3.8 times that in LVSI negative ones. Besides, positive lymph node status was also proved to be independently associated with LVSI. These results are consistent with previous large-population-based findings. According to a research based on American National Cancer Database, the presence of LVSI increased the risk of regional LNM by 3 to 16 times in stage T1 patients [8]. Besides, Creasman et al. [9] recently analyzed the data of 5,045 endometrial cancer patients from the Gynecology Oncology Group (GOG) 210 study database with documented LVSI status, and also proved that LVSI was a risk factor for both pelvic and para-aortic LNM.

However, as to the influence of LVSI on recurrence and survival time, there is still controversy in research findings. An early study reviewed 240 patients receiving surgery in MD Anderson Cancer Center in 5 years and demonstrated that LVSI was associated with disease recurrence and shorter OS in grade 1–2, FIGO stage IA patients [10]. Recently, a multicenter study from France got similar results and proved that the prognostic influence of LVSI was independent of lymph node status [11]. Nevertheless, there are still several studies showing results opposite to the mainstream view. Neal and coworkers [16] found, by analyzing cases from Medical University of South Carolina, that after adjusting for other factors, LVSI was not predictive of either shorter recurrence-free survival (RFS) or shorter OS in lymph node negative endometrial cancer patients. Since all these researches were based on retrospective data and had similar sample size, it is hard to get a final conclusion as to the exact role of LVSI in endometrial cancer patients' survival.

In contrast to Western studies, most researches from Asian groups found negative results [17-20]. Studies from Thailand, Korea and Japan all demonstrated that LVSI did not contribute to disease recurrence [17-19]. In a recent multicenter study from Turkey, LVSI was not a prognostic factor for OS after recurrence in low risk EEC patients [20]. Since the analysis of our data from Chinese population yielded similar results, we doubt whether

there is a regional difference as to the survival influence of LVSI. Another possible reason for this result is that Chinese doctors tend to give adjuvant therapy more actively in LVSI positive patients, as is shown in our data (**Table 1**), which may balance the negative effects of LVSI. However, after controlling adjuvant therapy use and other adverse prognostic factors with multivariate Cox regression or propensity score matching, LVSI still could not bring additional survival risk to EEC patients. So, it seems that there are still some other factors working here. And if the regional difference does exist, then the risk stratification system proposed by Western researchers may not be truly suitable for Asian populations, and some adjustments may be needed accordingly.

Relevant data from China is quite limited, but several researches published recently supported our findings. Zhu et al. [26] in their paper analyzed 624 Chinese EEC patients with intermediate risk (grade 1–2, myometrial invasion <50%, tumor diameter <2 cm). Interestingly, though LVSI was found to be associated with LNM, all 15 cases with subsequent recurrence in this cohort were negative for LVSI. Another 2 Chinese-patient-based studies concluded that LVSI was not an independent risk factor for ovarian or pulmonary metastases [27,28], both of which are usually considered indicators of poorer prognosis. Our data also demonstrated that LVSI does not increase the risk of adnexal involvement. In our sample, however, the rate of positive LVSI was significantly higher in stage IV cases than in those of earlier stages, yet the number of stage IV patients here (6 in total) is too little to be convincing.

Currently, the risk stratification system for endometrial cancer in China are mainly based on evidences from Western studies, and the guidelines of Chinese Medical Association (CMA) and Chinese Society of Clinical Oncology (CSCO) both include LVSI as an indication for post-surgery adjuvant therapy. However according to the findings from our and some other groups, as mentioned above, LVSI was still not a well acknowledged risk factor in Chinese population. Chemo- and (or) radiotherapy given according to LVSI may cause a risk of overtreatment, which brings more adverse effects to the patients and higher economic burdens to the society. Taking our sample as an example, under the criteria of CMA risk stratification system, low risk patients will increase by approximately 4% when excluding LVSI as a risk factor. According to data from National Central Cancer Registry of China, there were 64,000 new endometrial cancer cases in 2014 [2], then an estimation is 1,600 new cases each year can dispense with adjuvant therapy if LVSI is omitted. With the increase of endometrial cancer incidence in China, the social-economic effects it brings will be greater in future years. In this sense, reevaluating current risk stratification system is necessary both for patient welfare and for more health economic benefits.

One strength of this work is that all surgeries and pathological evaluations were finished by specialists from our center, which grants the accuracy of all data. Besides, to our knowledge, among all Chinese-patient-based studies, we include the most LVSI positive cases. But there are still some shortcomings. Firstly, the retrospective nature of the study restricts our observation of patients' recurrence and survival status to a certain time period. Prospective studies are needed to observe the survival impact of LVSI in longer terms, and also to better control the interference of confounders, especially adjuvant therapy. Secondly, in this study all data are based on patients from a single center, more data from other centers and more multicenter studies are still needed to fully uncover related features of Chinese patients. Furthermore, Bosse et al. [7] analyzed the data of Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) trials retrospectively and found that substantial LVSI had much stronger prognostic value compared with focal LVSI. Since not all pathology

reports described LVSI in such detail, we did not manage to define and discuss different LVSI status (e.g. focal vs. substantial) separately here.

In this study, we preliminarily uncovered the prognostic features of LVSI positive EEC patients in China, and raised our doubt about the value of adjuvant therapy in these patients. But still, more studies are needed to see the whole picture. In the future, prospective cohorts with detailed grouping should be established to set LVSI to a proper place in the risk evaluation system of EEC, and also to further test the effect of different adjuvant therapy strategies on patients with distinct LVSI status. A detailed classification of different degrees of LVSI may be necessary for accurately understanding the role of it. Additionally, in this study we proposed prediction models for EEC patients' recurrence and survival. Some factors in the models, such as age, grade and peritoneal cytology, are currently not included in the FIGO staging system. Peritoneal cytology does not even appear in any risk stratification systems of Chinese or international guidelines. The prognostic value of these factors should be further verified by more studies of larger scales.

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