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Risk factors for pelvic lymph node metastasis in endometrial cancer

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Abstract

Purpose To evaluate the risk factors for pelvic lymph node metastasis (LNM) in endometrial cancer (EC).

Methods Clinicopathological characteristics and preoperative laboratory results were retrospectively analyzed in 393 surgically staged patients with EC (January 2014–February 2019).

Results Pelvic LNM was detected in 45 (11.5%) patients. Univariate analysis showed that increased preoperative levels of human epididymis protein 4 (HE4), carbohydrate antigen 125 (CA125), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR), and decreased absolute lymphocyte count (ALC), as well as non-endometrioid histology, grade 3 tumor, deep myometrial invasion, vaginal or para-uterine involvement, adnexal involvement, positive peritoneal cytology, and lymphovascular space invasion (LVSI) were risk factors for pelvic LNM (All $p < 0.05$). Multivariate analysis revealed that preoperative serum HE4 ≥ 132 pmol/L (odds ratio (OR) 4.25, 95% confidence interval (CI) 1.65–10.94, $p = 0.003$), serum CA 125 ≥ 27.6 U/mL (OR 6.10, 95% CI 2.31–16.07, $p = 0.000$), non-endometrioid histology (OR 16.64, 95% CI 5.96–46.47, $p = 0.000$), myometrial invasion ≥ 50% (OR 5.30, 95% CI 2.07–13.55, $p = 0.001$), positive peritoneal cytology (OR 4.70, 95% CI 1.21–18.27, $p = 0.025$), and LVSI (OR 3.11, 95% CI 1.09–8.92, $p = 0.034$) remained as independent risk factors for pelvic LNM in EC. With the increase of these independent risk factors, the rate of pelvic LNM was increased significantly.

Conclusions Higher preoperative levels of serum HE4 and CA125, non-endometrioid histology, deep myometrial invasion, positive peritoneal cytology, and LVSI are independent risk factors for pelvic LNM in EC, which can provide scientific basis for lymphadenectomy.

Keywords Endometrial cancer · Pelvic lymph node metastasis · Risk factors · Carbohydrate antigen 125 · Human epididymis protein 4

Introduction

Endometrial cancer (EC) is one of the most common malignancies in the female reproductive system [1]. The rising incidence of EC has raised consideration. For example, in China, there were about 63,400 new cases and 21,800 deaths of EC in 2015 [2]. Lymph node metastasis (LNM) is one of the major metastatic modalities in EC, which is closely related to poor prognosis [3, 4]. It has been reported that the incidence of LNM ranges from 10.5 to 14.9% in patients with EC [5–7].

Since 1988, the International Federation of Gynecology and Obstetrics (FIGO) has revised the clinical staging of EC to surgical pathological staging, and taken the pelvic and para-aortic LNM as one of the staging criteria [8]. Currently, the routine surgical procedure for EC staging and treatment is total hysterectomy and bilateral salpingo-oophorectomy, with pelvic and para-aortic lymphadenectomy, in many clinics around the world [3, 9, 10]. However, the therapeutic value of routine lymphadenectomy remains controversial. As vaginal bleeding is generally associated with EC, most patients are diagnosed at an early stage [3] and lymphadenectomy does not appear to improve overall survival or recurrence-free survival in patients with early EC, according to the results of two large randomized controlled trials [11, 12]. In addition, patients undergoing lymphadenectomy are even more likely to experience surgery-related systemic diseases or lymphedema/lymphocyst formation [13]. The above evidence suggests that routine lymphadenectomy may be

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unnecessary or even overtreatment for EC patients. Therefore, to predict the risk of LNM before surgical intervention is of great clinical value.

To prevent overtreatment and complications from lymphadenectomy in EC patients, risk factors for LNM should be identified to distinguish the patients who are more likely to benefit from lymphadenectomy from others. Currently, some risk factors associated with LNM of EC have been reported, including elevated serum carbohydrate antigen 125 (CA125) levels, tumor diameter > 2 cm, grade 3 tumor, deep myometrial invasion, adnexal involvement, lymphovascular space invasion (LVSI), positive peritoneal cytology, etc., [6, 7, 14–16]. However, up to now, whether preoperative laboratory results such as serum levels of human epididymis protein 4 (HE4), sialic acid (SA) and carcinoembryonic antigen (CEA), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR) are the risk factors for LNM in EC has not been reported yet.

The purpose of this study was to determine the risk factors of pelvic LNM from the clinicopathological characteristics and preoperative laboratory results of patients with EC to provide valuable clinical guidance for making decision of lymphadenectomy and guide the individualized treatment of patients.

Materials and methods

Data of EC patients undergoing surgical treatment between January 2014 and February 2019 in the Department of Gynecology, Affiliated Hospital of Qingdao University in China were retrospectively analyzed. This study protocol was approved by our hospital ethics committee.

The surgical treatment for EC included total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Before operation, serum concentrations of HE4, CA125, CEA, SA, and blood routine test were performed. Patients who received preoperative adjuvant therapy (such as radiotherapy, chemotherapy or hormone therapy), combined with infectious diseases or other malignant tumors were excluded. Patients with incomplete medical records were also excluded.

Patients' data were collected by reviewing medical records, operation records, preoperative laboratory results and postoperative pathological reports. The clinicopathological characteristics of patients were recorded, including age at surgery (years), body mass index (BMI, kg/m^2), histological type (endometrioid or non-endometrioid), FIGO tumor grade (grade 1, grade 2 or grade 3), tumor size (cm), depth of myometrial invasion (< 50% or ≥ 50%), vaginal or para-uterine involvement (yes or no), adnexal involvement (yes or no), peritoneal cytology (positive or negative), LVSI (yes or no), and lymph node metastatic status. The following preoperative laboratory results were also collected: levels of serum HE4 (pmol/L), CA125 (U/mL), CEA (ng/mL) and SA (mg/dL), absolute neutrophil count (ANC, 10^9/L), absolute lymphocyte count (ALC, 10^9/L), absolute monocyte count (AMC, 10^9/L), white blood cell count (WBC, 10^9/L), platelet count (PLT, 10^9/L), and hemoglobin concentration (Hb, g/L). Moreover, neutrophil to lymphocyte ratio (NLR, = ANC/ALC), PLR (= PLT/ALC), and MLR (= AMC/ALC) were calculated and recorded. Surgical pathological staging was performed using the 2009 FIGO criteria [17].

Statistical analysis was performed using Statistical Package for the Social Sciences version 22.0 software (SPSS Inc, Chicago, IL, USA). The Shapiro–Wilk test was used to test the distribution of normality. In univariate analysis, the Mann–Whitney *U* test for continuous variables (because they're not normally distributed) and the Chi-square or Fisher's exact tests for categorical variables were used. The optimal cut-off value was determined by means of receiver operating characteristic (ROC) curve. Multivariable logistic regression analysis was used to identify independent risk factors. Variables with p value < 0.05 in univariate analysis were included in multivariate analysis. p value < 0.05 (two-sided) was considered statistically significant.

Results

Clinicopathological characteristics of EC patients

Pelvic lymphadenectomy was performed in all 393 EC patients enrolled by this study, 305 (77.6%) of them underwent para-aortic lymphadenectomy at the same time. 50 cases (12.7%, 50/393) were detected to have LNM, among them, 30 cases of isolated pelvic LNM, 15 cases of both pelvic and para-aortic LNM, and 5 cases of isolated para-aortic LNM, respectively.

Median age at surgery of the patients was 56 years (range 25–80 years) and median BMI was 26.03 kg/m^2 (range 17.57–43.55 kg/m^2). 314 (79.9%) patients had stage I, 11 (2.8%) had stage II, 59 (15.0%) had stage III, and 9 (2.3%) had stage IV disease. 331 (84.2%) patients were detected to have endometrioid histology whereas 62 (15.8%) had non-endometrioid histology. 67 (17.0%) patients were with FIGO grade 1 tumors, 211 (53.7%) with grade 2 tumors, and 115 (29.3%) with grade 3 tumors. The median tumor size was 3 cm (range 0.5–12 cm). Myometrial invasion ≥ 50% was detected in 115 (29.3%) patients, vaginal or para-uterine involvement in 13 (3.3%) patients, adnexal involvement in 28 (7.1%) patients, positive peritoneal cytology in 24 (6.1%) patients, and LVSI in 42 (10.7%) patients, respectively (Table 1).

Table 1 Clinicopathological characteristics of EC patients

Characteristics	Median (range)/*n* (%)
Age at surgery (years)	56 (25–80)
BMI (Kg/m^2)	26.03 (17.57–43.55)
Stage	
I	314 (79.9%)
II	11 (2.8%)
III	59 (15.0%)
IV	9 (2.3%)
Histological type	
Endometrioid	331 (84.2%)
Non-endometrioid	62 (15.8%)
Tumor grade	
Grade 1	67 (17.0%)
Grade 2	211 (53.7%)
Grade 3	115 (29.3%)
Tumor size (cm)	3 (0.5 ~ 12)
Myometrial invasion	
< 50%	278 (70.7%)
≥ 50%	115 (29.3%)
Vaginal or para-uterine involvement	
Yes	13 (3.3%)
No	380 (96.7%)
Adnexal involvement	
Yes	28 (7.1%)
No	365 (92.9%)
Peritoneal cytology	
Negative	369 (93.9%)
Positive	24 (6.1%)
LVSI	
Yes	42 (10.7%)
No	351 (89.3%)
Lymph node metastasis	50 (12.7%)
Isolated pelvic LNM	30
Isolated para-aortic LNM	5
Pelvic + para-aortic LNM	15

EC endometrial cancer, *BMI* body mass index, *LVSI* lymphovascular space invasion, *LNM* lymph node metastasis

Univariate analysis of risk factors for pelvic LNM in EC

Pelvic LNM was detected in 45 (11.5%) patients. In addition to 5 patients with isolated para-aortic LNM, a total of 388 patients were finally included in the analysis. Univariate analysis showed that preoperative levels of serum HE4 ($p = 0.000$), serum CA125 ($p = 0.000$), MLR ($p = 0.011$), and PLR ($p = 0.006$) were all higher, while ALC ($p = 0.004$) was lower in the pelvic LNM-positive group than those of without LNM group. The risk of pelvic LNM significantly increased in patients with non-endometrioid histology ($p = 0.000$), grade 3 tumor ($p = 0.000$), tumor size ≥ 3 cm ($p = 0.000$), myometrial invasion ≥ 50% ($p = 0.000$), vaginal or para-uterine involvement ($p = 0.000$), adnexal involvement ($p = 0.000$), positive peritoneal cytology ($p = 0.000$), and LVSI ($p = 0.000$). However, there was no difference in age, BMI, CEA, SA, ANC, AMC, WBC, PLT, Hb, and NLR between the two groups (All $p > 0.05$) (Table 2).

Multivariate analysis of risk factors for pelvic LNM in EC

According to the ROC curve analysis, the optimal cut-off values of serum HE4, serum CA125, ALC, MLR, and PLR for pelvic LNM were 132 pmol/L, 27.6 U/mL, 1.67×10^9/L, 0.19 and 166, respectively. These optimal cut-off values were used for further multivariate analysis.

Multivariate analysis revealed that preoperative serum HE4 ≥ 132 pmol/L (odds ratio (OR) 4.25, 95% confidence interval (CI) 1.65–10.94, $p = 0.003$), serum CA 125 ≥ 27.6 U/mL (OR 6.10, 95% CI 2.31–16.07, $p = 0.000$), non-endometrioid histology (OR 16.64, 95% CI 5.96–46.47, $p = 0.000$), myometrial invasion ≥ 50% (OR 5.30, 95% CI 2.07–13.55, $p = 0.001$), positive peritoneal cytology (OR 4.70, 95% CI 1.21–18.27, $p = 0.025$) and LVSI (OR 3.11, 95% CI 1.09–8.92, $p = 0.034$) were independent risk factors for pelvic LNM in patients with EC (Table 3).

When the number of independent risk factors was 0, the incidence rate of pelvic LNM was 0.0%. With the increase of these independent risk factors, the rate of pelvic LNM increased significantly ($p < 0.05$) (Table 4).

Discussion

In our study, the incidence of LNM was only 12.7% (50/393), but more than 80% of patients underwent unnecessary lymph node dissection. Therefore, it is important to predict the probability of LNM depending on risk factors and to prevent unnecessary lymph node resection.

Our results show that serum HE4 ≥ 132 pmol/L, serum CA 125 ≥ 27.6 U/mL, non-endometrioid histology, myometrial invasion ≥ 50%, positive peritoneal cytology, and LVSI were independent risk factors for pelvic LNM (Table 3). With the increase of these independent risk factors, the risk of pelvic LNM was increased significantly (Table 4). Therefore, preoperative detection of serum HE4 and CA125 levels, preoperative diagnostic curettage for determining the histological type, imaging examination or intraoperative naked eye observation for assessing the depth of myometrial invasion, peritoneal cytology examination, and even intraoperative frozen pathological examination are very important methods to help doctors for the decision of lymphadenectomy in patients with EC. In addition, we found that in 305

Table 2 Univariate analysis of risk factors for pelvic LNM in EC

Variables	Groups		*P*
	Negative LNM	Positive pelvic LNM	
Cases	343	45	
Age (years)	55 (51, 62)	57 (53, 63)	0.239
BMI (Kg/m^2)	26.17 (23.83, 28.80)	25.22 (23.09, 27.50)	0.071
HE4 (pmol/L)	71.90 (51.87, 100.80)	108.70 (67.00, 258.60)	0.000
CA125 (U/mL)	18.89 (12.74, 31.48)	55.89 (28.09, 228.95)	0.000
CEA (ng/mL)	1.50 (0.96, 2.22)	1.48 (0.92, 2.32)	0.889
SA (mg/dL)	61.00 (54.82, 66.00)	62.85 (58.78, 66.00)	0.076
ANC (10^9/L)	3.25 (2.58, 4.06)	3.07 (2.47, 4.00)	0.673
AMC (10^9/L)	0.34 (0.28, 0.42)	0.34 (0.28, 0.43)	0.844
ALC (10^9/L)	1.85 (1.53, 2.25)	1.60 (1.27, 2.00)	0.004
WBC (10^9/L)	5.76 (4.79, 6.69)	5.41 (4.39, 6.58)	0.235
PLT (10^9/L)	252 (212, 294)	244 (209, 281)	0.858
Hb (g/L)	134 (123, 141)	128 (119, 140)	0.243
NLR	1.71 (1.30, 2.23)	1.88 (1.45, 2.51)	0.069
MLR	0.18 (0.15, 0.23)	0.21 (0.17, 0.28)	0.011
PLR	132 (102, 172)	166 (122, 208)	0.006
Histological type			0.000
Endometrioid	310	20	
Non-endometrioid	33	25	
Tumor grade			0.000
Grade 1 or 2	263	14	
Grade 3	80	31	
Tumor size (cm)			0.000
<3	147	3	
≥ 3	196	42	
Myometrial invasion			0.000
$<50\%$	266	10	
$\geq 50\%$	77	35	
Vaginal or para-uterine involvement			0.000
No	338	38	
Yes	5	7	
Adnexal involvement			0.000
No	329	32	
Yes	14	13	
Peritoneal cytology			0.000
Negative	330	34	
Positive	13	11	
LVSI			0.000
No	319	28	
Yes	24	17	

LNM lymph node metastasis, *EC* endometrial cancer, *BMI* body mass index, *HE4* human epididymis protein 4, *CA125* carbohydrate antigen 125, *CEA* carcinoembryonic antigen, *SA* sialic acid, *ANC* absolute neutrophil count, *AMC* absolute mononuclear cell count, *ALC* absolute lymphocyte count, *WBC* white blood cell count, *PLT* platelet count, *Hb* hemoglobin concentration, *NLR* neutrophil to lymphocyte ratio, *MLR* monocyte to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *LVSI* lymphovascular space invasion

patients undergoing systemic lymphadenectomy, 45.5% (15/33) of patients with pelvic LNM also had para-aortic LNM, while only 1.6% (5/305) of patients with isolated para-aortic LNM. So, it is suggested that pelvic and para-aortic lymphadenectomy should be performed simultaneously in high-risk patients with pelvic LNM.

Table 3 Logistic multivariate analysis of risk factors for pelvic LNM in EC

Variables	Comparison group	Control group	OR	95% CI	*P*
HE4 (pmol/L)	≥ 132	< 132	4.25	1.65–10.94	0.003
CA125 (U/mL)	≥ 27.6	< 27.6	6.10	2.31–16.07	0.000
ALC (10^9/L)	< 1.67	≥ 1.67			NS
MLR	≥ 0.21	< 0.21			NS
PLR	≥ 166	< 166			NS
Histological type	Non-endometrioid	Endometrioid	16.64	5.96–46.47	0.000
Tumor grade	Grade 3	Grade 1 or 2			NS
Tumor size (cm)	≥ 3	< 3			NS
Myometrial invasion	≥ 50%	< 50%	5.30	2.07–13.55	0.001
Vaginal or para-uterine involvement	Yes	No			NS
Adnexal involvement	Yes	No			NS
Peritoneal cytology	Positive	Negative	4.70	1.21–18.27	0.025
LVSI	Yes	No	3.11	1.09–8.92	0.034

LNM lymph node metastasis, *EC* endometrial cancer, *CA125* carbohydrate antigen 125, *HE4* human epididymis protein 4, *ALC* absolute lymphocyte count, *MLR* monocyte to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *LVSI* lymphovascular space invasion, *NS* nonsignificant

Table 4 The rate of pelvic LNM under different independent risk factors

Number of risk factors	Patients (metastatic/total)	Pelvic LNM rate (%)
0	0/154	0.0
1	3/117	2.6
2	11/58	19.0[ab]
3	15/41	26.6[abc]
4	7/9	77.8[abcd]
5	8/8	100.0[abcd]
6	1/1	100.0[ab]

Independent risk factors: HE4 ≥ 132 pmol/L, CA125 ≥ 27.6 U/mL, non-endometrioid histology, myometrial invasion ≥ 50%, positive peritoneal cytology, and LVSI

LNM lymph node metastasis, [a]compared with the group with zero risk factor, $p < 0.05$, [b]compared with the group with one risk factor, $p < 0.05$, [c]compared with the group with two risk factors, $p < 0.05$, [d]compared with the group with three risk factors, $p < 0.05$

In recent years, many models have been established to predict LNM of EC, but none of them has been widely accepted and applied in clinical practice. Ideally, a risk assessment model that can accurately predict the probability of LNM should be designed. Based on this model, patients with low risk of LNM can be identified, and better suggestions made for surgical options to reduce overtreatment and complications associated with lymphadenectomy. On the contrary, systemic lymphadenectomy is recommended for patients with high risk of LNM. Anton et al. proposed a model containing preoperative serum CA125 to assess LNM in patients with EC [14]. In this model, the authors proposed that the cut-off value of preoperative CA125 was 21.5 U/mL, which was similar to our study (27.6 U/mL). Their study concluded that the risk of LNM ranged from 2.7% in patients with myometrial invasion < 50%, no LVSI, image negative lymph nodes and CA125 level < 21.5 U/mL to 82.3% when all four parameters were positive. In our study, serum CA125 ≥ 27.6 U/mL, serum HE4 ≥ 132 pmol/L, non-endometrioid histology, myometrial invasion ≥ 50%, positive peritoneal cytology, and LVSI were independent risk factors for pelvic LNM. The incidence of pelvic LNM was 0.0% in the absence of the above 6 factors, while the incidence was 100% in the presence of more than four risk factors (Table 4). When none of these independent risk factors is present, patients without pelvic LNM can be screened out and lymphadenectomy is not recommended. Certainly, further external validation is required. In addition, Wang et al. showed that the preoperative level of serum HE4 in patients with LNM was significantly higher than those without LNM [18]. Our study shows that preoperative serum HE4 was one of the independent risk factors for pelvic LNM in EC patients, and that the risk of pelvic LNM in patients with HE4 ≥ 132 pmol/L were 4.25 times compared to that in those with HE4 < 132 pmol/L (Table 3).

In addition, inflammation is closely related to the occurrence and development of tumors, and tumor microenvironment is largely coordinated by inflammatory cells [19]. Common inflammatory cells in peripheral blood include neutrophils, lymphocytes, monocytes. Abu-Shawer et al. found that ANC, AMC, NLR, and PLR may have potential application value in predicting prognosis and distant metastasis through the study of FIGO stage III and stage IV gynecological (endometrial, ovarian, and cervical) cancers [20]. However, Kadan et al. thought that NLR was not a reliable predictor of LNM in low-risk EC [21]. In our study,

univariate analysis showed that the positive group of pelvic LNM had lower ALC ($p=0.004$) than that of negative group, while MLR ($p=0.011$) and PLR ($p=0.006$) were higher. But, there was no evidence showing that ANC, AMC, WBC, PLT, and NLR were associated with pelvic LNM (all $p>0.05$). We considered that lymphopenia may be caused by tumor metastasis that destroys the integrity of the lymphatic system.

Recently, studies on sentinel lymph node biopsy for the prediction of LNM in EC patients are ongoing. Sentinel lymph node dissection may be useful for the management of EC, but it is still in the experimental stage and needs to be further studied [22, 23]. Therefore, we should constantly explore more effective predictors of LNM, to provide better theoretical support for the scientific decision of lymphadenectomy for patients with EC.

In conclusion, our study suggested that preoperative serum CA125 ≥ 27.6 U/mL, serum HE4 ≥ 132 pmol/L, non-endometrioid histology, myometrial invasion ≥ 50%, positive peritoneal cytology, and LVSI were independent risk factors for pelvic LNM in patients with EC. With the increase of these risk factors, the rate of pelvic LNM was increased significantly, providing a scientific basis for lymphadenectomy in the patients with EC.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval This study was approved ethically by the Affiliated Hospital of Qingdao University (Qingdao, China). Informed consent was waived because of a retrospective study.

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