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A novel multivariable prediction model for lymphatic dissemination in endometrioid endometrial cancer: The lymph node Metastasis Risk Index

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ABSTRACT

Objective: The purpose of this study was to develop a risk assessment index that could determine which endometrioid endometrial cancer (EC) patients would benefit from a lymphadenectomy.
Methods: The final pathology reports of 353 women who underwent complete surgical staging, including pelvic and para-aortic lymphadenectomy, for endometrioid EC between January 2008 and June 2018 were retrospectively reviewed. A logistic regression was used to investigate the clinicopathological factors associated with a positive nodal status. The independent risk factors for lymphatic dissemination were used to build a risk model and a "Lymph Node (LN) Metastasis Risk Index" was defined as follows: (tumor grade) × (primary tumor diameter) × (percentage of myometrial invasion) × (preoperative serum CA 125 level). The scores used in the LN Metastasis Risk Index were weighted according to the odds ratios assigned for each variable. The diagnostic performance of the model was expressed as the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio.
Results: The LN Metastasis Risk Index correctly identified 35 of 40 LN-positive women at a cutoff point of 981.0 (sensitivity: 87.5%, specificity: 86.3%, negative predictive value: 98.2%, positive predictive value: 44.9%, positive likelihood ratio: 6.37, and negative likelihood ratio: 0.14). The area under the receiver operating characteristic curve was 0.90 (95% confidence interval = 0.858–0.947) at this cutoff. The clinical accuracy of the model was 86.4%. When a cutoff point of <981.0 was selected in order to define those women at low-risk for lymphatic dissemination, our prediction model classified 275 women (77.9%) as being at low-risk for nodal involvement. Among these 275 women, 5 actually had positive LNs, which indicated a 1.8% false-negative rate.
Conclusion: After external validation, the LN Metastasis Risk Index may be a valuable tool for the surgical management of endometrioid EC.

Introduction

The criteria defining the necessity for a lymph node (LN) dissection in patients with endometrial cancer (EC) have been introduced by the Mayo Clinic Algorithm [1], which is based on an intra-operative frozen section (IFS) analysis. The widely accepted tumor factors that indicate the deferral of lymphadenectomy in endometrioid EC include an International Federation of Gynecology and Obstetrics (FIGO) grade 1 or 2 histology, myometrial invasion (MMI) of <50%, and a primary tumor diameter (PTD) of ≤2 cm [1,2], as well as no MMI, regardless of the tumor grade and tumor size [3]. Women with these features are accepted as having a low-risk for LN metastasis [1,2]. However, approximately 75% of the patients with EC require lymphadenectomy when using the Mayo Clinic Algorithm [1,4]; even though the rate of LN involvement is approximately 15% in endometrioid EC cases [5].

A recent study examining the final pathology reports of patients with endometrioid EC showed that approximately two thirds of the patients managed intra-operatively according to the Mayo criteria were exposed to unnecessary lymphadenectomy [5]. Based on this background information, we wondered whether uterine factors, such as percentage of MMI, tumor grade, and tumor size, in addition to preoperative serum cancer antigen 125 (CA 125) level, could help to define a risk index that could identify endometrioid

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EC patients who actually require systematic lymphadenectomy. Therefore, the purpose of this retrospective study was to develop a "LN Metastasis Risk Index" that could determine which endometrioid EC patients would benefit from a lymphadenectomy based on the development of a prediction model.

Materials and methods

The data of all of the women with EC who received primary surgical treatment with curative intent at Zekai Tahir Burak Women's Health Training and Research Hospital in Ankara, Turkey between January 2008 and June 2018 were extracted retrospectively from our prospectively maintained ECdatabase. All of the patients provided informed consent regarding the research use of their medical information upon admission. This study was approved by the Institutional Review Board of our hospital.

The final pathology reports of 966 women with EC who underwent surgery were analyzed. Those women with final histopathological diagnoses of pure endometrioid histology were included in the study.Women with non-endometrioid tumors were excluded, as well as those patients with mixed histologies. We also excluded women with PTDs that were not applicable due to a diffuse endometrial surface spread only, those who received neoadjuvant chemotherapy, and those with other primary synchronous malignancies, as well as those with incomplete medical records. The women whose final pathology reports recorded the depth of MMI as just <50% or ≥50% were also excluded. These women were excluded because their final pathology reports did not provide information about the exact percentage of MMI. In addition, women who underwent hysterectomy only, without lymphadenectomy, and those who received only pelvic lymphadenectomy were excluded, as well as those women who underwent inadequate lymphadenectomy.

Certified gynecological oncologists performed all of the operations. The primary surgery included a total hysterectomy ± bilateral salpingo-oophorectomy (BSO) with pelvic and para-aortic lymphadenectomy. A lymphadenectomy was performed at the discretion of the attending surgeon until January 2013 (until that time, an IFS analysis was not a routine procedure at our institution); however, it was performed according to an IFS analysis thereafter. Pelvic and para-aortic lymphadenectomy was performed as previously described [6]. An adequate lymphadenectomy was considered to be at least 10 pelvic and 5 para-aortic LNs removed, as suggested by AlHilli et al. [7].

The histological data were obtained from the primary pathologist's report, and no central pathology review was performed. Experienced gynecological pathologists analyzed and interpreted all of the surgical specimens. The pathological features [histology, grade, MMI, PTD, and lymphovascular space invasion (LVSI)] and the methodology regarding the pathological examination have been described previously [6,8].

Each patient's age and preoperative serum CA 125 level were abstracted from the patient's files. The following data were recorded by abstracting the tumor characteristics from the original pathology reports: the PTD [as a continuous variable or dichotomous (<30 mm or ≥30 mm, and <40 mm or ≥40 mm, respectively)), percentage of MMI (defined by the MMI depth from the endomyometrial junction to the deepest focus of the myoinvasive carcinoma divided by the overall myometrial thickness), the FIGO grade, the stage, and LVSI (positive or negative). The 2009 FIGO staging system was employed for tumor staging [9].

Since LVSI [10] and preoperative serum CA 125 level [11,12] have been identified as independent risk factors for LN involvement in EC, the LN Metastasis Risk Index was founded on these two variables (LN Metastasis Risk Index = LVSI x preoperative serum CA 125 level). Based on the fact that LVSI can only be determined precisely after a full pathological review of a hysterectomy specimen [13], we recently defined the "tumor grade x PTD x MMI percentage" triad as the "Risk of LVSI Index," and we demonstrated that the Risk of LVSI Index may be used as a substitute for LVSI [14] in endometrioid EC. Therefore, the LN Metastasis Risk Index was defined as follows: (tumor grade x PTD x MMI percentage) x preoperative serum CA 125 level. The LN Metastasis Risk Index was calculated for each patient, and our model was designed to predict LN metastasis, regardless of the disease stage. Additional information about building the LN Metastasis Risk Index is presented in detail in the Results section.

The statistical analyses were performed using IBM SPSS Statistics for Macintosh (version 22; IBM Corp., Armonk, NY, USA). The data were expressed as the median and range for the continuous variables, and the binary variables were reported as the count and percentage. A simple logistic regression analysis was performed in order to determine the correlation of the tumor characteristics with a positive LN status. Those variables with p values of less than 0.05 were included in the multiple logistic regression analysis. The impact of each variable on the positive nodal status was evaluated, and a p value of <0.05 was considered to indicate statistical significance.

The predictive accuracy of the model was assessed according to its discrimination (i.e., the ability of the model to differentiate patients with positive LNs from those without). The discrimination was measured using a receiver operating characteristic (ROC) curve, and it was summarized by the area under the curve (AUC). The diagnostic performance of the model was expressed as the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio. It was stratified according to the level of diagnostic confidence, and it was reported according to the Standards for the Reporting of Diagnostic Accuracy [15].

Results

During the course of the study, 966 women underwent surgery for EC. Those patients with non-endometrioid or mixed tumors (n = 206), those who received neoadjuvant chemotherapy (n = 2), those with synchronous malignancies (n = 2), and those with incomplete medical records (n = 5) were excluded. Additionally, those women with PTDs that were not applicable due to diffuse endometrial surface spread only (n = 3) and those whose final pathology reports recorded the MMI depth as just <50% or ≥50% (n = 250) were not included in the study. We also excluded those women who underwent a total hysterectomy ± BSO only (n = 104), those who received a pelvic lymphadenectomy only (n = 18), and those with inadequate lymphadenectomy (n = 23). Therefore, three hundred and fifty-three patients were included in the final analysis.

The median age of the patients at diagnosis was 58.0 years old (range: 31–84 years). Among all of the patients, 207 (58.6%) had grade 1 tumors, 100 (28.3%) had grade 2 tumors, and 46 (13.0%) had grade 3 tumors. The median MMI percentage was 33.0% (range: 0%–100%). The MMI was ≥1/2 in 121 (34.3%) patients, and there were 91 (25.8%) women with LVSI. Overall, 40 patients (11.3%) had at least one LN metastasis. The clinicopathological features of the patients included in the study are shown in Table 1, and Table 2 demonstrates the comparison of the clinicopathological characteristics with regard to the LN status.

The univariate analysis revealed that the LN metastasis risk was significantly increased in patients with a preoperative serum CA 125 level of≥ 35 U/ml ($p < 0.001$), a PTD of ≥40 mm ($p < 0.001$), MMI of >1/3 ($p < 0.001$), and grade 2 or 3 tumors ($p < 0.001$) (Table 3). In the multivariable analysis, a PTD of ≥40 mm [odds ratio (OR) = 2.39, 95% confidence interval (CI) = 1.02–5.62,

Table 1
Clinicopathological features of 353 women with endometrioid endometrial cancer undergoing complete surgical staging including pelvic and para-aortic lymph node dissection.

Characteristics	Values
Age at surgery, median, (min-max), years	58.0 (31–84)
Stage, n (%)	
I	278 (78.8%)
II	16 (4.5%)
III	45 (12.7%)
IV	14 (4.0%)
Grade, n (%)	
Grade 1	207 (58.6%)
Grade 2	100 (28.3%)
Grade 3	46 (13.0%)
LVSI, n (%)	
LVSI negative, n (%)	262 (74.2%)
LVSI positive, n (%)	91 (25.8%)
PTD, mm, median, (min-max)	30 (1–130)
PTD, n (%)	
<40 mm	227 (64.3%)
≥40 mm	126 (35.7%)
MMI, median, %	33%
MMI < 1/2, n (%)	232 (65.7%)
MMI ≥ 1/2, n (%)	121 (34.3%)
Lymph nodes (LNs)	
Total number removed [median(range)]	54 (18–166)
Total pelvic LNs removed [median(range)]	36 (10–110)
Total para-aortic LNs removed [median(range)]	16 (5–61)

Abbreviations: n: Number; LVSI: lymphovascular space invasion; PTD: primary tumor diameter; MMI: myometrial invasion; LN: lymph node.

Table 2
Comparison of clinicopathological characteristics of women with endometrioid endometrial cancer undergoing surgery with regard to lymph node metastasis.

	LN negative n = 313	LN positive n = 40	p
Age, years (median, range)			
Age	58 (31–84)	58.5 (43–75)	0.16
Age≤60 years (%)	198 (63.3%)	22 (55.0%)	
Age>60 years (%)	115 (36.7%)	18 (45.0%)	0.386
PTD, mm (median, range)			
PTD	30.0 (1–130)	47.5 (10–110)	<0.001
PTD < 30 mm (%)	146 (46.6%)	4 (10.0%)	
PTD ≥ 30 mm (%)	167 (53.4%)	36 (90.0%)	<0.001
PTD < 40 mm (%)	217 (69.3%)	10 (25.0%)	
PTD ≥ 40 mm (%)	96 (30.7%)	30 (75.0%)	<0.001
MMI			
MM ≤ 1/3 (%)	168 (53.7%)	3 (7.5%)	
MMI > 1/3 (%)	145 (46.3%)	37 (92.5%)	<0.001
Grade			
Grade 1 (%)	198 (63.3%)	9 (22.5%)	
Grade 2 or 3 (%)	115 (36.7%)	31 (77.5%)	<0.001
LVSI			
LVSI negative	260 (83.1%)	2 (5.0%)	
LVSI positive	53 (16.9%)	38 (95.0%)	<0.001
Baseline Serum CA 125			
<35 U/ml	273 (87.2%)	18 (45.0%)	
≥35 U/ml	40 (12.8%)	22 (55.0%)	<0.001

Abbreviations: LN: lymph node; n: number; PTD: primary tumor diameter; MMI: myometrial invasion; LVSI: lymphovascular space invasion.

p = 0.045], MMI of >1/3 (OR = 5.17, 95% CI = 1.44–18.59, p = 0.012), grade 2 or 3 disease (OR = 3.96, 95% CI = 1.63–9.65, p = 0.002), and a preoperative serum CA 125 level of ≥35 U/ml (OR = 5.97, 95% CI = 2.66–13.37, p < 0.001) were defined as independent risk factors for LN metastasis in women with endometrioid EC (Table 3). In the formulization of the LN Metastasis Risk Index, we adhered strictly to the previously described original scores for PTD and tumor grade defined in the Risk of LVSI Index, which was introduced in our previous study [14]. The rationale for this choice was to consider LVSI as a "separate" parameter in the prediction of LN involvement, and to replace it with the Risk of LVSI Index. An OR of 2.39 for tumors with a PTD of ≥40 mm, as demonstrated by the multivariate analysis of the present cohort (Table 3), shows the risk for LN metastasis, not the risk for a positive LVSI status. The same is valid for the tumor grade. An OR of 3.96 for grade 2 or 3 tumors, as assessed by the multivariate analysis of the present cohort (Table 3), shows the risk for LN metastasis, not the risk for a positive LVSI status. Based on this information, we strictly adhered to the previously described original scores for PTD and tumor grade according to the Risk of LVSI Index [14], and we used a score of 5 for grade 2 or 3 tumors and a score of 3 for those tumors with a PTD of ≥30 mm. The MMI percentage was represented as an absolute number. Those cases with no MMI were scored as 0 because no MMI, regardless of the tumor grade and tumor size, has been reported to be associated with a lymphatic dissemination rate of 0% in previous studies [3,5]. The cutoff value for the preoperative serum CA 125 level was determined as 35 U/ml because the ROC curve associated with preoperative serum CA 125 level showed the highest sensitivity and specificity at 35 U/ml for detecting a positive LN status in our study population (data not shown). A baseline serum CA 125 level of < 35 U/ml was scored as 1, whereas a baseline serum CA 125 of ≥35 U/ml was indicated with a score of 6 (the most significant predictor of LN involvement in our cohort) (Table 3). Finally, the LN Metastasis Risk Index was built as follows: (a score of 3 for tumors with a PTD of ≥30 mm, or a score of 1 for tumors with a PTD of <30 mm) × (a score of 5 for grade 2 or 3 tumors, or a score of 1 for grade 1 tumors) × [the absolute percentage of MMI (a score of 0 for women with no MMI)] × (a score of 6 for women with a preoperative serum CA 125 level of ≥35 U/ml, or a score of 1 for women with a preoperative serum CA 125 level of <35 U/ml).

According to the LN Metastasis Risk Index suggested in this study, the presence of positive LNs was correctly estimated in 35 of 40 node-positive women at a cutoff point of 981.0 (sensitivity of 87.5%, specificity of 86.3%, NPV of 98.2%, PPV of 44.9%, positive likelihood ratio of 6.37, and negative likelihood ratio of 0.14). When the ROC curve analysis of the model was performed, the AUC was 0.903 at this cutoff (95% CI = 0.858–0.947, p < 0.001) (Fig. 1). The clinical accuracy of the model was found to be 86.4%.

When a cutoff point of <981.0 was selected in order to define those women at low-risk for lymphatic dissemination, the LN Metastasis Risk Index classified 275 women (77.9%) as being at low-risk for LN involvement. Among these 275 women, five actually had positive LNs, which indicated a 1.8% false-negative rate.

Discussion

This study developed a risk assessment index in order to predict the probability of lymphatic dissemination in women with endometrioid EC. The principle findings of this study indicated that the LN Metastasis Risk Index had a diagnostic performance of detecting a positive nodal status at a cutoff of 981.0 with 87.5% sensitivity and 86.3% specificity, while the PPV and NPV of the model were 44.9% and 98.2%, respectively. Our prediction model worked well with an AUC of 0.90 at a cutoff of 981.0, and its clinical accuracy was 86.4%.

However, some limitations of our study deserve attention, such as its retrospective, single-institutional design, as well as the lack of a central pathology review. The relatively low rate of lymphatic dissemination in our study seems to decrease the power of the statistical analysis, whereas the lack of external validation limits the generalizability of our findings.

Although the currently available guidelines suggest evaluation of nodal status in the surgical management of EC [16,17], the therapeutic value of lymphadenectomy in EC is still an issue of debate [18]. In spite of retrospective studies suggesting that

Table 3
Univariate and multivariate analyses of women with endometrioid endometrial cancer undergoing complete surgical staging with regard lymph node involvement.

	Cases (LN[+])	Univariate Analysis p	Multivariate Analysis		
			OR	95% CI	p
Age, years					
≤60	22/220 (10.0%)				
>60	18/133 (13.5%)	0.386			
PTD					
<40 mm	10/227 (4.4%)				
≥40 mm	30/126 (23.8%)	<0.001	2.39	1.02–5.62	0.045
MMI					
≤1/3	3/171 (1.7%)				
>1/3	37/182 (20.3%)	<0.001	5.17	1.44–18.59	0.012
Grade					
1	9/207 (4.3%)				
2 or 3	31/146 (21.2%)	<0.001	3.96	1.63–9.65	0.002
Serum Ca 125					
<35 U/ml	18/291 (6.1%)				
≥35 U/ml	22/62 (35.4%)	<0.001	5.97	2.66–13.37	<0.001

Abbreviations: LN[+]: lymph node positive; OR: odds ratio; CI: confidence interval; PTD: primary tumor diameter; MMI: myometrial invasion.

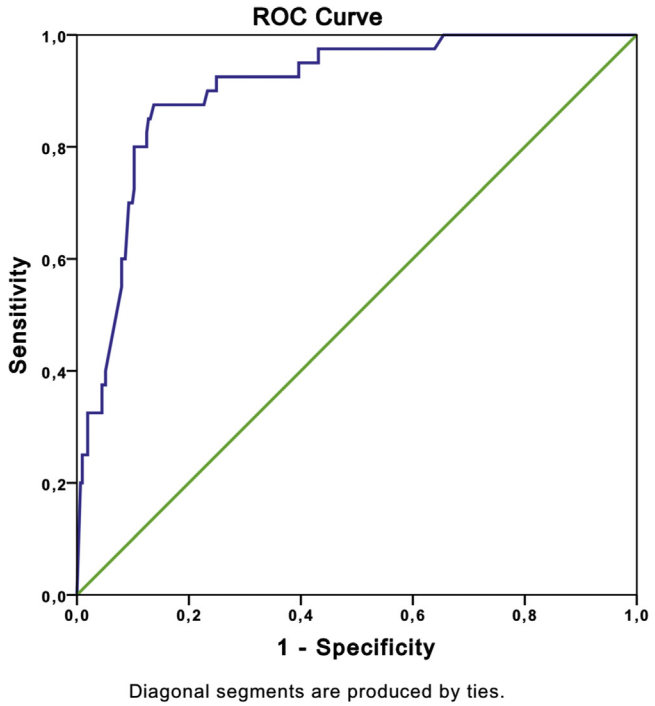

Fig. 1. The receiver-operating characteristics curve for the Lymph Node Metastasis Risk Index in women with endometrioid endometrial cancer.

lymphadenectomy may be therapeutic and improve outcomes [19,20], two randomized trials demonstrated no therapeutic value of lymphadenectomy in presumed (clinical) stage I EC [21,22]. However, many authors [23,24] have criticized these two randomized trials because of several methodological flaws. Today, it is broadly accepted that LN status still represents one of the most important prognostic factors based on which the adjuvant treatment is tailored [25–27].

Although a large part of the gynecological oncology community is currently moving towards a "sentinel lymph node (SLN) biopsy only" concept, the majority of the available data suggesting that SLN mapping is associated with similar oncological outcomes when compared to a standard lymphadenectomy come from retrospective studies in which the SLN biopsy was followed by a systematic pelvic ± para-aortic lymphadenectomy [28–30]. It should be emphasized that there are currently no prospective trials confirming the oncological safety of SLN biopsy only when compared to a standard lymphadenectomy [18]. Due to the lack of mature data on the oncological safety of the SLN biopsy only concept, prospective data are warranted before integrating SLN biopsy only as the standard of care in the surgical management of EC.

The rationale for the LN Metastasis Risk Index suggested in this study is simple. It is based mainly on two variables: LVSI, which has been reported to be the strongest predictor of LN metastasis in EC [10], and the preoperative serum CA 125 level, which has already been defined as an independent risk factor for lymphatic dissemination in EC [11,12]. However, because LVSI can only be determined precisely after a full review of a hysterectomy specimen [13], we decided to include the Risk of LVSI Index (tumor grade x PTD x MMI percentage) [14] in our prediction model as a substitute for LVSI. Based on this information, our prediction model has gained the ability for use in an intra-operative setting through a frozen section. This is the main strength of our prediction model when compared with previously described nomograms [13,31–33], which all included LVSI as a postoperative pathological feature so that they may only be useful in the management of EC patients who have already undergone hysterectomy without lymphadenectomy.

The performance of a prediction model for LN metastasis is mainly dependent on two important criteria: its false negative rate and its ability to identify the largest group of patients with a low risk of lymphatic dissemination [34]. Although the previously described prediction models provided a more individualized estimation of LN metastasis [13,31,35–39], they all assigned a small proportion of patients (5.4%–37.6%) to the low-risk group. Moreover, they generally suffered from compromised specificity rates, which resulted in a large number of unnecessary lymphadenectomies. However, the LN Metastasis Risk Index proposed in the current study seemed to perform better than the previous postoperative models that predicted lymphatic dissemination in endometrioid EC (Table 4).

The nodal count is the most important condition that needs to be satisfied in order to assess the predictive value of a model for lymphatic dissemination [33]. However, several previous studies [13,36,37] suffered from low number of LNs removed. It should be emphasized that all of the patients included in the present study underwent pelvic and para-aortic LN dissection with a systematic lymphadenectomy rate of 100%.

The clinical applicability of a prediction model is crucial [40]. A prediction model should be simple, easy to apply, and inexpensive. The complex nature of a prediction model can render it difficult to use in routine practice [40]. Our model depends on certain pathological features of the primary hysterectomy specimen, such

Table 4
Comparison of the current study with the previously published post-operative prediction models studying endometrioid endometrial cancer.

Author	Outcome provided by the model	Stage of disease for inclusion	Number of patients	LNM rate	AUC	False negative rate	Patients assigned to the low-risk group
Creasman et al. [35] (GOG criteria)	LNM probability	Clinical stage I	330	39/380 (11.8%)	0.76	0/18 (0%)	18/330 (5.4%)
Kamura et al. [37]	LNM probability	Any FIGO stage	316	41/316 (13.0%)	0.72	NR	NR
Mariani et al. [1] (Mayo clinic algorithm)	LNM probability	Clinical stage I and II	182	28/182 (15.4%)	0.75	1/39 (2.6%)	39/182 (21.4%)
Zhang et al. [38]	Binary results	Clinical stage I and II	285	46/285 (16.1%)	NR	2/67 (3.0%)	67/285 (23.5%)
Milam et al. [36]	LNM probability	Any FIGO stage	283	28/283 (9.9%)	0.73	0/24 (0%)	24/283 (8.4%)
Akbayir et al. [39]	Binary result	Clinical stage I and II	229	36/229 (15.7%)	NR	3/86 (3.5%)	86/229 (37.6%)
Pollom et al. [13]	LNM probability	Any FIGO stage	296	38/296 (12.8%)	0.83	NR	NR
Current Study	Binary result	Any FIGO stage	353	40/353 (11.3%)	0.90	3/249 (1.2%)	249/353 (70.5%)

Abbreviations: LNM: lymph node metastasis; FIGO: AUC: area under the receiver operating characteristic curve; NR: not reported.

as the tumor size, tumor grade, and percentage of MMI, which can also be assessed intra-operatively in a frozen section analysis. However, the MMI percentage that was used in the present study is not used in everyday practice [41], but it can be easily integrated as a parameter to be studied, instead of an MMI of<50% or ≥50%. Additionally, our prediction model includes a baseline serum CA 125 level, which is widely available. Based on this, we believe that the LN Metastasis Risk Index suggested in this study is simple and easy to apply because it is founded on four well-known parameters.

The strengths of this study lie in the large number of patients with similar demographic characteristics and a uniform endometrioid histology, the detailed analysis of various clinicopathological factors that might have an impact on LN metastasis, the performance of uniform staging procedures with the same qualified gynecological oncologists, and the 100% systematic lymphadenectomy rate.

The LN Metastasis Risk Index seems to be a practical and easy prediction model that could serve as a clinically valid instrument for performing lymphadenectomy in only an appropriate group of patients in order to avoid overtreatment. Based on this, clinicians can adequately balance the risks and benefits on an individual basis, particularly for women with elevated surgical risks. Moreover, the LN Metastasis Risk Index seems to have a good clinical accuracy of 86.4%. However, the reader should note that our findings were dependent on the final pathology results. It is obvious that the accuracy rate of a frozen section analysis would determine the real diagnostic performance of our model in an intra-operative setting when the LN Metastasis Risk Index is used intra-operatively in daily clinical practice.

After external validation, the LN Metastasis Risk Index may be a valuable tool for the surgical management of endometrioid EC. However, future work is essential for analyzing the performance of the LN Metastasis Risk Index in a prospective fashion.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest with regard to this research.

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