A nomogram prediction model for lymph node metastasis in endometrial cancer patients

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Abstract

Background: The determination of lymph node(LN) status is critical for evaluating prognosis and identifying the necessity of adjuvant therapy of endometrial cancer(EC) patients. However, the significance of systematic lymphadenectomy remains controversial. This study aimed to explore the risk factors for lymph node metastasis(LNM) in patients with EC and develop a clinically useful nomogram based on clinicopathological parameters to predict it.

Methods: A total of 1517 consecutive patients who underwent staging surgery for EC were abstracted from Qilu Hospital of Shandong University. Parameters including patient-related, tumor-related, and preoperative hematologic examination-related were analyzed by univariate and multivariate logistic regression to determine the correlation with LNM. Based on the multivariate results, a nomogram was constructed and underwent further validation to predict the probability of LNM.

Results: The nomogram was constructed and incorporated valuable parameters from the final multivariate model including histological type, histological grade, depth of myometrial invasion, LVSI, cervical involvement, parametrial involvement, and HGB levels. The nomogram was cross-validated internally by the 200 bootstrap sample and showed good discrimination accuracy with an AUC of 0.899.

Conclusions: We developed and validated a 7-variable nomogram with a high concordance probability to predict the risk of LNM in patients with EC.

Introduction

Endometrial cancer(EC) is the most common gynecologic malignancy, especially in developed countries, with the incidence was about 12.9/100,000[1]. Approximately 70% of EC patients are diagnosed with stage I, and the overall prognosis is favorable, the 5-year survival rate of the patient of stage I was reported ranging from 74 to 91%. However, the metastasis is related to a worse outcome, the 5-year survival rate is 57–66% for stage III, stage IV is only 20–26%[2, 3].

Surgery is the primary intervention for EC which mainly based on total hysterectomy and bilateral salpingo-oophorectomy[4]. Indications for lymphadenectomy remain controversial. Proponents argued that systemic lymph node(LN) resection is necessary for determining the extent of the lesion, accurate staging, directing opportune adjuvant therapy, and it is also a predictive tool for assessing patient prognosis. But this view was challenged by several large-scale clinical randomized controlled trials[5–7], which suggested that patients in the early stage may not get survival benefits from lymphadenectomy. Opponents claimed that with the removal of LN, there is an increased incidence of some complications, such as lymphocyst, lymphoedema, deep vein thrombosis, and intestinal obstruction and so on. Given this, the National Comprehensive Cancer Network (NCCN) guidelines emphasized the importance of assessing risk factors for lymph node metastasis(LNM) preoperatively and intraoperatively, and suggested an individualized and tailored LN dissection way[8].

For the risk assessment of LNM, it is widely accepted that the “Mayo clinic criteria”, low risk refers to endometrioid-type, tumor histology grade I or II, 50% or less myometrial invasion depth, and tumor diameter of 2 cm or less[9]. However, this evaluation criterion was criticized against the accuracy of the frozen section, and it is difficult to achieve uniform quality monitoring.

Nomogram is a graphic calculation tool which has been proposed to visualize and individualize prediction under different situation[10, 11]. This study aimed to develop a clinically useful nomogram to predict the LNM in patients with EC by several clinicopathological parameters to help clinicians better screen out high-risk groups and develop appropriate treatment plans.

Patients And Methods

Study cohort

In this retrospective study, a total of 1517 consecutive patients who underwent staging surgery including hysterectomy, pelvic lymphadenectomy (more than 10 LN removed) with or without para-aortic lymphadenectomy for EC were abstracted from Qilu Hospital of Shandong University. The current study was approved by the Qilu Hospital Ethics Committee. All the patients did not receive other treatments such as radiotherapy, chemotherapy or hormones before surgery. Patients with sarcoma, carcinosarcoma, leiomyosarcoma, a double primary tumor, or other metastatic cancer were excluded. Clinicopathological parameters were collected and determined as followed: patient-related characteristics (age at diagnosis, gestation, production, abortion, symptoms before diagnosis including abnormal vaginal fluid and abnormal vaginal bleeding, comorbidities including endocrine and cardiovascular diseases, history of smoking, history of and drinking, menopause), tumor characteristics (histological type, histological grade, FIGO stage, depth of myometrial invasion, lymphovascular invasion(LVSI), cervical involvement, and parametrial involvement) and the results of preoperative hematologic examination (white blood cell(WBC) count, red blood cell(RBC) count, hemoglobin(HGB), blood platelet(PLT), lymphocyte, albumin/globulin ratio, total cholesterol, and triglyceride). The histological grade and clinical stage were classified according to the 2009 FIGO staging criteria[4].

Construction of nomogram

Parameters including patient-related, tumor-related, and preoperative hematologic examination-related were analyzed by univariate and multivariate logistic regression to determine the correlation with LNM. Variable without statistical significance were excluded as predictive variables for the nomogram. The correlation results were described by the odds ratio (OR) and corresponding 95% confidence interval (CI). Type I error rate was taken as 0.25 for candidate variables for multivariate logistic regression. The receiver operating characteristic (ROC) curve was plotted and the area under the curve (AUC) was calculated to determine the predicted value of clinical variables. An AUC of 1.0 reflects ideal concordance, while an AUC of 0.5 represents no relationship. The agreement between the observed outcome and the predicted values was studied using two calibration curves. $P < 0.05$ indicates that the difference was

statistically significant. Based on the multivariate Cox analysis results, a nomogram integrating the valuable independent clinicopathological variables was constructed to predict for LNM.

Establishment and validation of the nomograms by R software

Internal validation of the nomogram was conducted via a bootstrap method with 200 resamples to get relatively unbiased estimates. Concordance index (c-index) was used to evaluate the accuracy of the prediction.

Statistical analysis

All the variables were analyzed by a two-sided statistical test including χ^2 and Student *t* test.Univariate and multivariate Cox regression analyses were performed using SPSS 20. R software package was used to perform the nomogram. $P < 0.05$ indicates that the difference was statistically significant.

Results

Patient and clinical characteristics

The overall data from the 1517 patients who met the inclusion criteria were analyzed. The median age of all patients at the time of surgery was 55 years (range, 21–82 years). 105(6.29%) patients had LNM. Among them, 74(4.87%) patients had pelvic LNM, 5(0.33%) patients had para-aortic LNM, and 26(1.71%) patients had both pelvic and para-aortic LNM, respectively. The majority of patients were diagnosed with endometrioid EC(1376/1517,90.70%). We collected some other detailed patient information including symptoms before diagnosis, comorbidities, menstrual history, reproductive history, pathological parameters and several results of preoperative hematologic examinations(Table 1).

Table 1
Patient characteristics.

	Non-LN metastases	LN metastases	*P value*
	1412	105	
Age at surgery			0.002
Median(mean)	55(54.42)	57(57.15)	
Range	21–80	36–82	
Gestation			0.630
Median(mean)	3(2.73)	3(2.80)	
Range	0–13	1–6	
Production			0.134
Median(mean)	2(1.82)	2(1.99)	
Range	0–12	1–5	
Abortion			0.327
Median(mean)	1(0.92)	1(0.81)	
Range	0–7	1–4	
Symptoms			0.691
Yes	1306	96	
No	106	9	
Comorbidities			0.164
Yes	561	49	
No	851	56	
History of smoking			0.226
Yes	11	2	
No	1401	103	
History of drinking			0.302
Yes	4	1	
No	1408	104	
Menopause			0.238

	Non-LN metastases	LN metastases	*P value*
Yes	831	68	
No	581	37	
FIGO			
I	1225		
II	113		
III	64	92	
IV	10	13	
Histologic type			< 0.001
Endometrioid	1313	63	
Non-endometrioid	99	42	
Histologic grade			< 0.001
Well differentiated	651	11	
Moderate/poor differentiated	761	94	
Depth of myometrial invasion			< 0.001
50	1147	41	
≥ 50	265	64	
LVSI			< 0.001
Present	110	37	
Not reprted	1302	68	
Cervical involvement			< 0.001
Yes	129	31	
No	1283	74	
Parametrial involvement			< 0.001
Yes	9	15	
No	1403	90	
WBC(mean,×109/L)	6.06	6.74	0.118
RBC(mean,×109/L)	4.40	4.23	0.001
PLT(mean,×109/L)	269.29	283.97	0.052

	Non-LN metastases	LN metastases	*P value*
HGB(mean,g/l)	126.29	119.39	0.001
Lymphocyte(mean,×109/L)	1.94	1.65	0.573
Albumin/globulin ratio(mean)	1.65	1.55	< 0.001
Total cholesterol(mean,mmol/L)	5.00	4.70	0.004
Triglyceride(mean,mmol/L)	1.54	1.29	0.001
Abbreviations:			
LN = lymph node			
FIGO = International Federation of Gynecology and Obstetrics			
LVSI = lymphovascular invasion			
WBC = white blood cell			
RBC = white blood cell			
PLT = platelet			
HGB = hemoglobin			

Univariate and Multivariate Predictors for LNM

According the univariate analysis, age, histological type, histological grade, depth of myometrial invasion, LVSI, cervical involvement, parametrial involvement, HGB, albumin/globulin ratio, total cholesterol and triglyceride were all significantly associated with LNM, whereas other parameters were not. By multivariate logistic regression analysis, LVSI is the most predictive factor for LNM, patients with positive LVSI had 8.853-fold increased risk for LNM (95%CI:5.326–14.715; P < 0.001). In addition, histological type (OR: 3.195; 95%CI: 1.825–5.596; P < 0.001), histological grade (OR: 2.326; 95% CI: 1.157–4.676; P = 0.018), depth of myometrial invasion (OR: 2.362; 95% CI: 1.423–3.920; P = 0.001), parametrial involvement (OR: 7.77; 95% CI: 2.442–24.723; P = 0.001) and HGB (OR: 0.985; 95% CI: 0.972–0.997; P = 0.016) remained significant predictors of LNM, whereas cervical involvement was borderline significant (OR: 1.77; 95% CI: 0.978–3.203; P = 0.059,). Table 2 summarizes the results of the univariate and multivariate logistic regression analyses.

Table 2
Multivariate logistic regression analysis of the LN metastasis (n = 1517)

	OR	95%CI	*P value*
Histologic type	3.195	1.825–5.596	< 0.001
Histologic grade	2.326	1.157–4.676	0.018
Depth of myometrial invasion	2.362	1.423–3.920	0.001
LVSI	8.853	5.326–14.715	< 0.001
Cervical involvement	1.770	0.978–3.203	0.059
Parametrial involvement	7.770	2.442–24.723	0.001
HGB	0.985	0.972–0.997	0.016
Abbreviations:			
LN = lymph node			
FIGO = International Federation of Gynecology and Obstetrics			
LVSI = lymphovascular invasion			
WBC = white blood cell			
RBC = white blood cell			
PLT = platelet			
HGB = hemoglobin			

Construct a nomogram for the prediction risk of LNM

As shown in Fig. 1, the nomogram was constructed and incorporated clinical variables from the final multivariate model including histological type, histological grade, depth of myometrial invasion, LVSI, cervical involvement, parametrial involvement, and HGB levels. For individualized prediction, each predictor variables corresponded to a selectable value, the total point was calculated by a sum of all points corresponding to the patient's characteristics. Regarding the clinical application of this nomogram, we can take a patient with all of these adverse pathologic risk factors as an example, there would be a 95% chance of LNM.

Accuracy of the nomogram to predict LNM

The nomogram was cross-validated internally by the 200 repetitions of bootstrap sample corrections. For the prediction of LN involvement, the nomogram showed good discrimination accuracy with an AUC of 0.899 (95% CI: 0.870–0.927) (Fig. 2). The calibration plots showed in Fig. 3 represents how closely the

predictions from the nomogram compared with actual outcomes for the 1517 patients in this study. The value on the X axis represents nomogram prediction and value on the Y axis represents actual probability, while the diagonal dashed line stands for an exact matches between nomogram prediction and observed probability. Consequently, the calibration plots of this study demonstrated excellent agreements between nomogram estimation and actual probability.

Discussion

The LN is the most common place for extrauterine metastasis of EC, and the presence of LNM has been demonstrated to be the most important prognostic factor for EC. The risk of LNM account for 3–5% in patients with low-grade and superficially invasive EC, while it is approximately 16–22% for patients with high-grade disease[9, 12, 13]. The determination of LN status is critical for evaluating prognosis and identifying the necessity of adjuvant therapy. However, the significance of systematic lymphadenectomy remains controversial. There were some large-scale retrospective studies support the therapeutic significance of LN resection, especially for patients with intermediate-high risk factors[14–16]. However, several large-scale clinical randomized controlled trials suggested that patients may not get survival benefits from lymphadenectomy which presumed to be related with increased surgical complications[5, 7]. Thus, we believe that the decision to perform lymphadenectomy should be based on an accurate and individualized risk assessment for LNM.

Multivariate analysis can obtain the coefficient of relevant risk factors, and calculate the specific risk value through the model formula, but it is difficult to integrate the predicted value of these indicators[17, 18]. Recently, research scholars are getting increasingly interested in nomograms[19, 20], which is an intuitive and easily readable graphical chart based on the results by the logistic regression or Cox regression, it could accurately predict the probability of occurrence of an event. For clinical application, the nomogram could incorporate patient individual characteristics and need further validation by cross-validation and bootstrapping methods.

In the current study, we constructed a nomogram based on several clinicopathological parameters to predict the risk of LNM to guide clinical diagnosis and treatment. According to the multivariate logistic regression analysis, histological type, histological grade, depth of myometrial invasion, LVSI, cervical involvement, parametrial involvement, and HGB levels are significantly associated with LNM. The brief nomogram was built by the involvement of these seven competing risk models and the predictive accuracy and validity were determined. Specifically, the nomogram showed good discrimination accuracy with an AUC of 0.899 (95% CI: 0.870–0.927) and a mean error of less than 2% by validation examination. And we found that LVSI was the most convincing risk predictor for LNM. LVSI is an essential step in the process of metastatic spread of EC, it is also an important prognostic factor of EC. Mariani et al found that adjuvant therapy and lymphadenectomy may be necessary if LVSI was present[21]. Similarly, Pollom et al proposed an algorithm focusing on pathological and clinical parameters of 296 EC patients, they reported that the positive status of LVSI was significantly associated with LNM[22]. However, Bendifallah et al developed a nomogram based on the SEER database to evaluate the association of LNM with age,

race, histological subtype, histological grade, and depth of myometrium invasion. Nevertheless, the SEER database does not contain information about the patient's LVSI status, and we presume that the model lacking of LVSI information not comprehensive enough[23].

The determination of LVSI requires evaluation of hematoxylin and eosin (H&E)-stained slides under light microscopy. But it is a challenge for pathologists to determine whether LVSI exists and distinguish it from mimickers such as retraction artifacts. Immunohistochemical staining with CD31, D2-40 and cytokeratin was used to overcome the difficulty of diagnosis[24]. Although it is difficult to determine the presence or absence of LVSI before a hysterectomy, it is still feasible according to the intraoperative frozen section. Previously study showed that there was 92.4% overall agreement between the frozen section and postoperative pathology regarding the presence of LVSI[25]. The limitation of this study is that the LVSI status was evaluated based on the final postoperative pathology. Due to a large number of patients included in the study, we were unable to obtain all the frozen section to determine it intra-operation. But LVSI still has the predictive value especially for incidentally attained patients with EC after hysterectomy.

To be more intuitive and convenient to construct the nomogram, the histological type of EC was classified as endometrioid EC and non-endometrioid EC, and grade differentiation was divided into two categories: well differentiated and moderate/poor differentiated. We found that non-endometrioid EC is a valuable predictor for LNM, which was consistent with previous studies[26]. The special aggressive biological behavior of non-endometrioid EC made it significantly related with worse clinical outcomes. As for tumor grade, it is not considered as a risk factor by the Milwaukee risk stratification model by which lymphadenectomy can be quickly determined through gross examination of tumor diameter and depth of myometrial invasion[27]. However, it was still reported that tumor grade is a significant prognostic factor of EC and an independent predictor for LNM[28]. Our result was consistent with the former study, and we found a positive association between tumor grade and LNM. And we also found that cervical involvement and parametrial involvement was easier to see in patients with LNM, which indicated that the two parameters also have the predictive value for LNM.

The occurrence of malignant tumors is often accompanied by an increased probability of hematological abnormality. It has been demonstrated that systemic immune and inflammation responses play a vital role in the initiation and progression of the malignant tumor[29]. The metabolic diseases such as serum sex steroids or lipid levels disorders have emerged to be a non-negligible risk factor of EC, and the carcinogenic effect of metabolic abnormality was well established[30, 31]. To further uncover the potential relation between LNM and some hematologic parameters, all the patients in our study have a complete blood count and serum analysis of sex steroids and lipids for preoperative assessment. We collected some detail information including WBC, RBC, HGB, PLT, lymphocyte, albumin/globulin ratio, total cholesterol and triglyceride for the risk prediction. We found that HGB, albumin/globulin ratio, total cholesterol and triglyceride were all significantly associated with LNM by univariate analysis. However, when combining with other risk factors, albumin/globulin ratio, total cholesterol and triglyceride were not strong enough to predict LNM. According to the present nomogram, the level of HGB was found to be an independent risk factor in LNM. Our finding was consistent with the former study by Njolstad TS, by

which they found that preoperative anemia was significantly correlated with tumor progression and poor disease-specific survival[32]. The possible explanation may be that the observed anemia caused by vaginal bleeding induced the release of several paracrine signaling factors affecting erythropoiesis, such as the pro-inflammatory cytokines interleukin-1 and tumor necrosis factorα,which considered to be related with tumor progression and LNM[33].

To the best of our knowledge, this risk prediction model is based on the most comprehensive clinicopathologic parameters and the largest number of included patients in China. Our finding was in line with a dependable nomogram based on some clinical parameters including age, race, tumor grade, histological type, myometrial invasion and cervical stromal invasion, which performed a good discrimination and a reliable calibration to predict LNM[23]. However, there are still several limitations. First, this is a single-institution study. The application universality and prediction accuracy of the model will be affected by the differences between the tested patients and the model patients. Although bootstrap internal validation was used to mimic new patient cohorts, there is still a need for external validation to ensure the accuracy of the study. Second, most of parameters incorporated in our model can be determined at the frozen section, but the determination of LVSI status can not be judged immediately during surgery. Despite there are defective for predicting intra-operation, it is still helpful for a postoperative decision whether adjuvant therapy or secondary operation was necessary for incidentally attained EC patients. This model also requires a large sample of prospective controlled studies to verify accuracy and utility in the future. It is worth noting that the nomogram model only provides a predictive probability of LNM, the professional interpretation also required according to the individual situation.

Conclusions

We have developed a 7-variable nomogram with a high concordance probability to predict the risk of LNM in women with EC. The model may facilitate gynecological oncologists to calculate the incidence of LNM in the individual patient and make a multidisciplinary decision on whether lymphadenectomy is necessary by balancing the risks and benefits. The accumulation of more data and prospective studies are needed in the future to ensure its applicability and provide more accurate guidance for clinical treatment.

List Of Abbreviations

Abbreviations	Full name
Lymph Node	LN
Endometrial Cancer	EC
Lymph Node Metastasis	LNM
the National Comprehensive Cancer Network	NCCN
Lymphovascular Invasion	LVSI
White Blood Cell	WBC
Red Blood Cell	RBC
Hemoglobin	HGB
Blood Platelet	PLT
Odds Ratio	OR
Confidence Interval	CI
Receiver Operating Characteristic	ROC
Area Under the Curve	AUC
Concordance Index	C-index
Hematoxylin and Eosin	H&E
Declarations	
Ethics approval and consent to participate	
Institutional review board approval was obtained prior to data abstraction by Ethics Committee of Qilu Hospital of Shandong University and individual patient consent was also obtained.	
Consent for publication	
Consent for publication was obtained in this study.	
Availability of data and material	
The dataset supporting the conclusions of this article is available in the Qilu Hospital of Shandong University repository, could contact the corresponding author to obtain these data.	

Declarations

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization: Zhiling Wang; Methodology: Shuo Zhang; Formal analysis and investigation: Jiguang Tian; Writing - original draft preparation: Wenhui Li; Writing - review and editing: Zhiling Wang, Ting Liu; Funding acquisition: Ting Liu; Resources: Zhiling Wang; Supervision: Ting Liu.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: **Global cancer statistics**. *CA: a cancer journal for clinicians* 2011, **61**(2):69-90.
2. Siegel R, Naishadham D, Jemal A: **Cancer statistics, 2013**. *CA Cancer J Clin* 2013, **63**(1):11-30.
3. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz AP, Ngan HY, Pecorelli S: **Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer**. *Int J Gynaecol Obstet* 2006, **95 Suppl 1**:S105-143.
4. Pecorelli S: **Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium**. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2009, **105**(2):103-104.
5. group As, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK: **Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study**. *Lancet* 2009, **373**(9658):125-136.
6. Uccella S, Podratz KC, Aletti GD, Mariani A: **Re: Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial**. *J Natl Cancer Inst* 2009, **101**(12):897-898; author reply 898-899.

7. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, Angioli R, Tateo S, Mangili G, Katsaros D *et al*: **Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial**. *J Natl Cancer Inst* 2008, **100**(23):1707-1716.
8. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, Chon HS, Chu C, Cohn D, Crispens MA *et al*: **Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology**. *J Natl Compr Canc Netw* 2018, **16**(2):170-199.
9. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC: **Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary?** *Am J Obstet Gynecol* 2000, **182**(6):1506-1519.
10. Yang XG, Feng JT, Wang F, He X, Zhang H, Yang L, Zhang HR, Hu YC: **Development and validation of a prognostic nomogram for the overall survival of patients living with spinal metastases**. *J Neurooncol* 2019, **145**(1):167-176.
11. Jeong SH, Kim RB, Park SY, Park J, Jung EJ, Ju YT, Jeong CY, Park M, Ko GH, Song DH *et al*: **Nomogram for predicting gastric cancer recurrence using biomarker gene expression**. *Eur J Surg Oncol* 2020, **46**(1):195-201.
12. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, Podratz KC: **Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging**. *Gynecol Oncol* 2008, **109**(1):11-18.
13. Turan T, Hizli D, Sarici S, Boran N, Gundogdu B, Karadag B, Tulunay G, Kose MF: **Is it possible to predict para-aortic lymph node metastasis in endometrial cancer?** *Eur J Obstet Gynecol Reprod Biol* 2011, **158**(2):274-279.
14. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N: **Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis**. *Lancet* 2010, **375**(9721):1165-1172.
15. Katz LA, Andrews SJ, Fanning J: **Survival after multimodality treatment for stage IIIC endometrial cancer**. *Am J Obstet Gynecol* 2001, **184**(6):1071-1073.
16. Bristow RE, Zahurak ML, Alexander CJ, Zellars RC, Montz FJ: **FIGO stage IIIC endometrial carcinoma: resection of macroscopic nodal disease and other determinants of survival**. *Int J Gynecol Cancer* 2003, **13**(5):664-672.
17. Li Y, Cong P, Wang P, Peng C, Liu M, Sun G: **Risk factors for pelvic lymph node metastasis in endometrial cancer**. *Arch Gynecol Obstet* 2019, **300**(4):1007-1013.
18. Paik ES, Kim TJ, Choi CH, Kim BG, Bae DS, Lee JW: **Clinical outcomes of patients with clear cell and endometrioid ovarian cancer arising from endometriosis**. *J Gynecol Oncol* 2018, **29**(2):e18.
19. Shigemura K, Sung SY, Chen KC, Fujisawa M: **Comment for "nomogram establishment for surgery-related complications in partial nephrectomy"**. *Ann Transl Med* 2019, **7**(Suppl 3):S120.
20. Zhang H, Ma G, Du S, Sun J, Zhang Q, Yuan B, Luo X: **Nomogram for predicting cancer specific survival in inflammatory breast carcinoma: a SEER population-based study**. *PeerJ* 2019, **7**:e7659.

21. Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC: **Predictors of lymphatic failure in endometrial cancer**. *Gynecologic oncology* 2002, **84**(3):437-442.
22. Pollom EL, Conklin CM, von Eyben R, Folkins AK, Kidd EA: **Nomogram to Predict Risk of Lymph Node Metastases in Patients With Endometrioid Endometrial Cancer**. *Int J Gynecol Pathol* 2016, **35**(5):395-401.
23. Bendifallah S, Genin AS, Naoura I, Chabbert Buffet N, Clavel Chapelon F, Haddad B, Luton D, Darai E, Rouzier R, Koskas M: **A nomogram for predicting lymph node metastasis of presumed stage I and II endometrial cancer**. *Am J Obstet Gynecol* 2012, **207**(3):197.e191-198.
24. Alexander-Sefre F, Singh N, Ayhan A, Salveson HB, Wilbanks G, Jacobs IJ: **Detection of tumour lymphovascular space invasion using dual cytokeratin and CD31 immunohistochemistry**. *J Clin Pathol* 2003, **56**(10):786-788.
25. Karabagli P, Ugras S, Yilmaz BS, Celik C: **The evaluation of reliability and contribution of frozen section pathology to staging endometrioid adenocarcinomas**. *Arch Gynecol Obstet* 2015, **292**(2):391-397.
26. Colombo N, Creutzberg C, Amant F, Bosse T, Gonzalez-Martin A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR *et al*: **ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up**. *Int J Gynecol Cancer* 2016, **26**(1):2-30.
27. Cox Bauer CM, Greer DM, Kram JJF, Kamelle SA: **Tumor diameter as a predictor of lymphatic dissemination in endometrioid endometrial cancer**. *Gynecol Oncol* 2016, **141**(2):199-205.
28. Stalberg K, Kjolhede P, Bjurberg M, Borgfeldt C, Dahm-Kahler P, Falconer H, Holmberg E, Staf C, Tholander B, Avall-Lundqvist E *et al*: **Risk factors for lymph node metastases in women with endometrial cancer: A population-based, nation-wide register study-On behalf of the Swedish Gynecological Cancer Group**. *Int J Cancer* 2017, **140**(12):2693-2700.
29. Takahashi R, Mabuchi S, Kuroda H, Kozasa K, Yokoi E, Matsumoto Y, Kimura T: **The Significance of Pretreatment Thrombocytosis and Its Association With Neutrophilia in Patients With Surgically Treated Endometrial Cancer**. *Int J Gynecol Cancer* 2017, **27**(7):1399-1407.
30. Luo YZ, Yang Z, Qiu YL, Li XH, Qin LQ, Su QS, Mo WN: **Pretreatment triglycerides-to-high density lipoprotein cholesterol ratio in postmenopausal women with endometrial cancer**. *Kaohsiung J Med Sci* 2019, **35**(5):303-309.
31. Cao WM, Zheng YB, Gao Y, Ding XW, Sun Y, Huang Y, Lou CJ, Pan ZW, Peng G, Wang XJ: **Comprehensive mutation detection of BRCA1/2 genes reveals large genomic rearrangements contribute to hereditary breast and ovarian cancer in Chinese women**. *BMC Cancer* 2019, **19**(1):551.
32. Njolstad TS, Engerud H, Werner HM, Salvesen HB, Trovik J: **Preoperative anemia, leukocytosis and thrombocytosis identify aggressive endometrial carcinomas**. *Gynecol Oncol* 2013, **131**(2):410-415.
33. Chen Y, Zhang L, Liu WX, Liu XY: **Prognostic significance of preoperative anemia, leukocytosis and thrombocytosis in chinese women with epithelial ovarian cancer**. *Asian Pac J Cancer Prev* 2015, **16**(3):933-939.

Figures

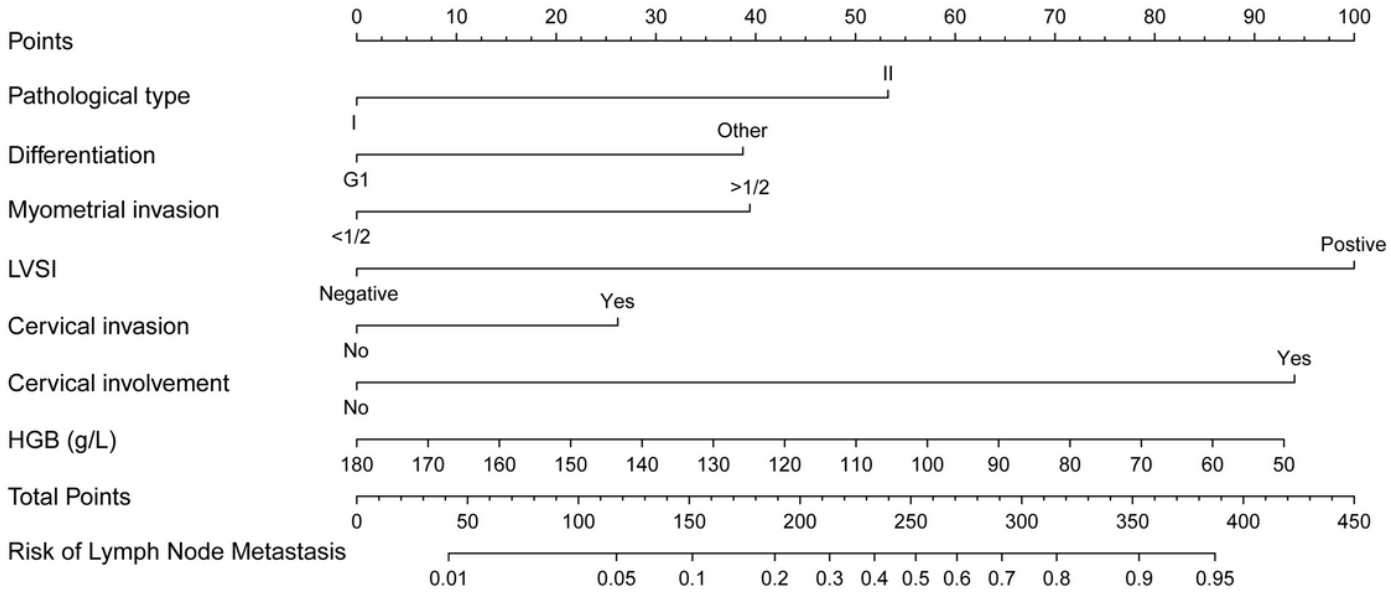

Figure 1

Nomogram predicting the probability of LNM for women with EC

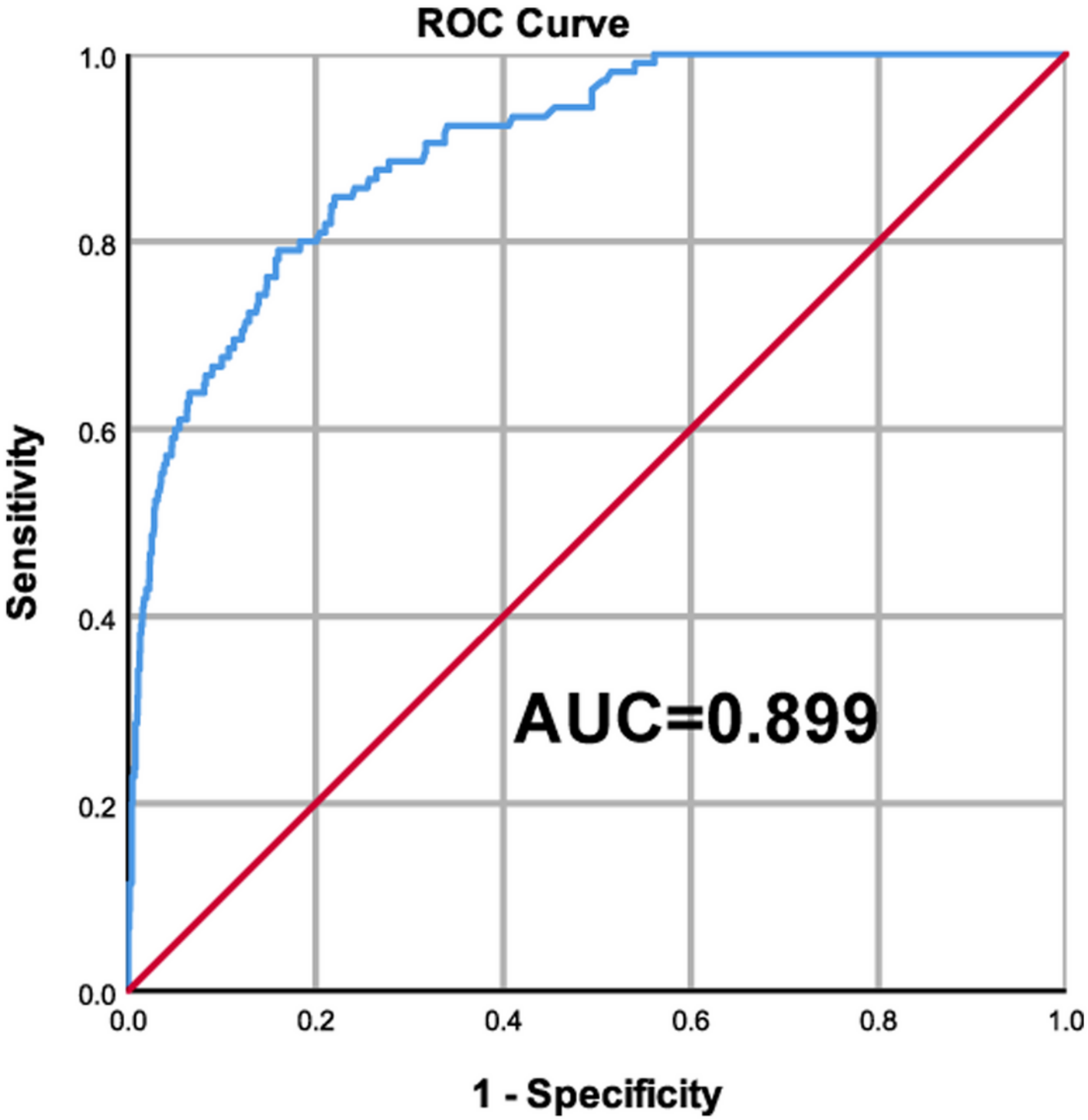

Figure 2

Receiver operating characteristic curves corresponding nomogram to predict LNM

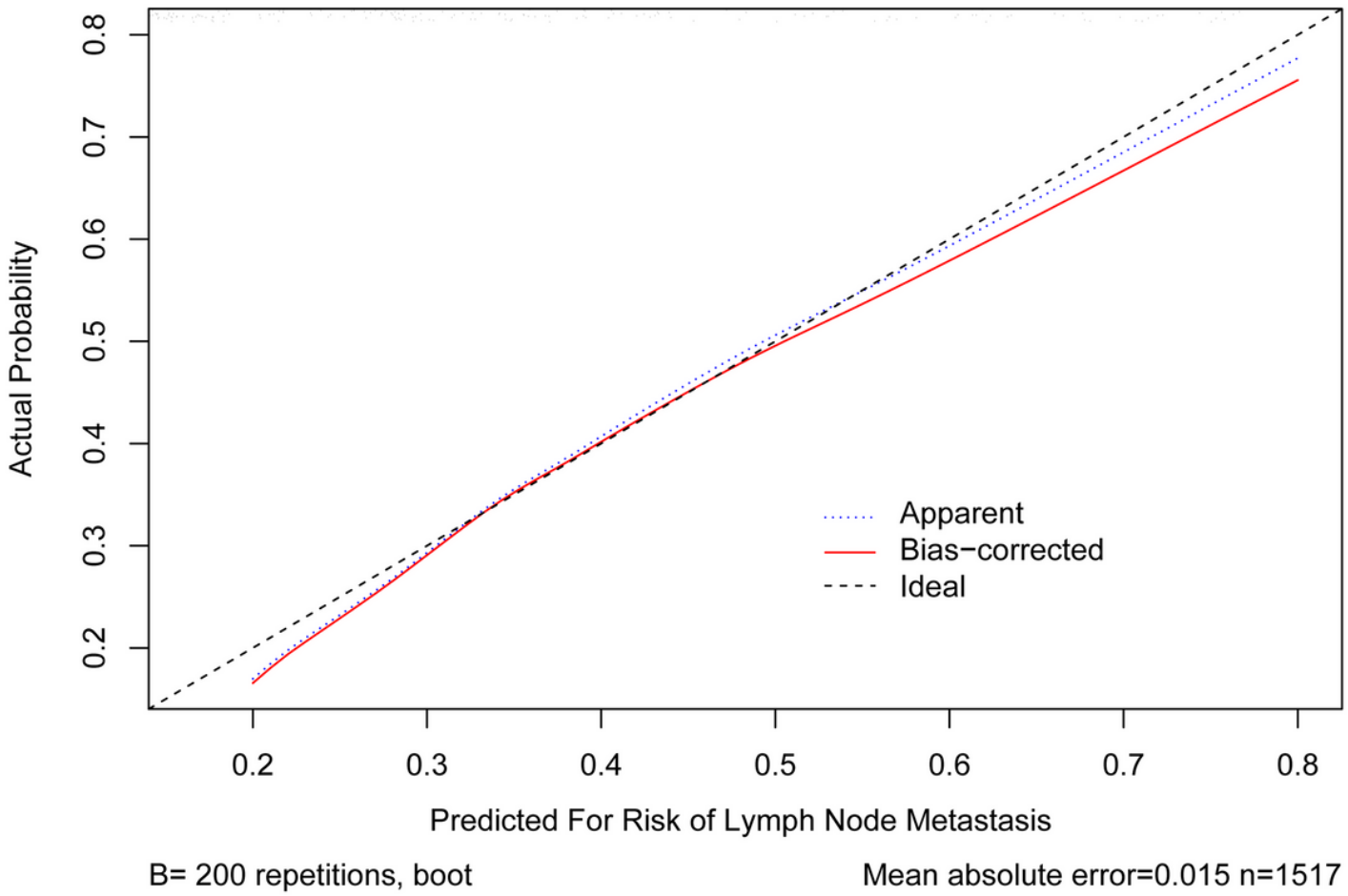

Figure 3

Internal calibration of the nomogram to predict LNM