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Original Article

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Constructing a prediction model for lymph node metastasis in patients with incidental finding of endometrial cancer based on Fully-Connected Network

Yuzhen Huang [1,2,*] **Qing Lin** [3,4,5,*] **Wei Liu** [1,2,*] **Yulan Ren** [6,*] **Huaying Wang** [6] **Zhiying Xu** [1,2] **Yu Xue** [1,2] **Wanying Zhou** [7] **Jiongbo Liao** [1,2] **Yiqin Wang** [1] **Weimin Tan** [7] **Bo Yan** [7] **Xiaojun Chen** [1,2,8]

[1]Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China
[2]Shanghai Key Laboratory of Female Reproductive Endocrine-Related Diseases, Shanghai, China
[3]Deep Neuro Cognition Lab, Institute for Infocomm Research (I2R), Agency for Science, Technology, and Research (A*STAR), Singapore
[4]Center for Frontier AI Research (CFAR), Agency for Science, Technology, and Research (A*STAR), Singapore
[5]School of Computer Science and Engineering, Nanyang Technological University, Singapore
[6]Fudan University Shanghai Cancer Center, Shanghai, China
[7]Shanghai Key Laboratory of Intelligent Information Processing, School of Computer Science, Fudan University, Shanghai, China
[8]Obstetrics and Gynecology Department, Tenth People's Hospital of Tongji University, Shanghai, China

ABSTRACT

Objective: Rare studies focused on patients with incidental diagnosis of endometrial cancer (EC) after hysterectomy. We intended to construct a prediction model of lymph node metastasis (LNM) based on Fully-Connected Network (FC Network) for these patients.
Methods: A total of 3,920 cases of EC that met the criteria from Obstetrics & Gynecology Hospital of Fudan University between January 2016 and February 2023 and 1995 cases from Fudan University Shanghai Cancer Center between January 2013 and October 2020 were retrospectively included for the construction of a predicting model which was based on FC Network. At the same time, 572 cases were prospectively collected for external validation.
Results: The sensitivity of the model was 0.946. Lympho-vascular space invasion, myometrial invasion, tumor grade, microcystic elongated and fragmented invasion, progesterone receptor, and cancer antigen 125 were used to construct a simplified nomogram. The area under the curve of the nomogram was 0.890 and 0.885 in validation and prospective cohorts, respectively.
Conclusion: The model we proposed has good sensitivity and can be used to predict the risk of LNM in patients with incidentally found EC. The simplified nomogram can be used as a substitute in certain situations. Based on another study, the threshold of 5% and 25% can be used for risk stratification.

Keywords: Endometrial Cancer; Fully-Connected Network; Lymph Node Metastasis; Machine Learning; Incomplete Surgical Staging

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Correspondence to
Xiaojun Chen
Obstetrics and Gynecology Hospital of Fudan University, No.419 Fangxie Road, Huangpu District, Shanghai 200021, China.
Email: xiaojunchen2013@sina.com

*Yuzhen Huang, Qing Lin, Wei Liu and Yulan Ren contribute equally to this work.

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ORCID iDs
Yuzhen Huang
https://orcid.org/0000-0003-1244-5579
Qing Lin
https://orcid.org/0000-0002-3808-3492
Wei Liu
https://orcid.org/0000-0001-8055-0317
Yulan Ren
https://orcid.org/0000-0001-9035-2218
Huaying Wang
https://orcid.org/0000-0002-5027-3838

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Zhiying Xu
https://orcid.org/0000-0003-0233-9713
Yu Xue
https://orcid.org/0000-0001-8431-2914
Wanying Zhou
https://orcid.org/0009-0007-3087-324X
Jiongbo Liao
https://orcid.org/0000-0002-1074-8245
Yiqin Wang
https://orcid.org/0000-0003-1138-7741
Weimin Tan
https://orcid.org/0000-0002-8179-1531
Bo Yan
https://orcid.org/0000-0002-5909-5855
Xiaojun Chen
https://orcid.org/0000-0002-5493-1500

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Conflict of Interest

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

Data Availability

The de-identified raw data of the cohorts in this study can be obtained from the corresponding author for research purposes and the code which was based on Fully-Connected Network was accessible from the corresponding author for reasonable request.

Author Contributions

Conceptualization: Y.B., C.X.; Data curation: H.Y., L.W., R.Y., W.H., X.Z., X.Y., L.J., W.Y.; Formal analysis: H.Y., L.W.; Funding acquisition: C.X.; Investigation: H.Y., L.Q., L.W., Z.W., C.X.; Software: L.Q., Z.W., T.W.; Supervision: R.Y., W.H., W.Y., T.W., Y.B., C.X.; Validation: L.Q.; Writing - original draft: H.Y.; Writing - review & editing: C.X.

Synopsis

This multicenter study included patients without evidence of extrauterine disease. Various imputation methods were compared to address missing data effectively. The model performed well in identifying patients with lymph node metastasis. A simplified nomogram was developed as a practical alternative to the full model.

INTRODUCTION

Endometrial cancer (EC) is a common gynecological cancer with a rising incidence globally, especially in high-income countries [1-3]. The mainstay treatment for EC is surgery currently. Accurate and complete surgical staging (total hysterectomy/bilateral salpingo-oophorectomy and lymph node assessment) significantly impacts patients' prognoses [4]. However, a proportion of patients with EC are incidentally found after surgical treatment for other benign indications. A retrospective study found 13 occult EC cases in a total of 6,981 hysterectomies [5]. Nine unexpected EC were found in 2,179 hysterectomies in another analysis [6]. The complete surgical staging was not performed which led to a lack of lymph nodes assessment. For early staged patients who have not undergone complete surgical staging, the subsequent treatment plan needs to be made based on the risk factors found in the uterus and the imaging findings according to the National Comprehensive Cancer Network guideline [7]. However, imaging has limitations in recognizing small metastatic lesions. Patients who had lymph node metastases were at high risk of recurrence without appropriate treatment, affecting their prognoses. Therefore, it is important to accurately predict the probability of lymph node metastasis (LNM) in these patients with accidental findings of EC.

Many studies have made efforts to construct models for predicting LNM in EC. A retrospective study used 7 factors to construct a nomogram to predict LNM in EC [8]. Despite having good predictive validity, the study cohort focused on patients with EC who underwent standard surgical staging. Another study also used digital histopathological images of primary EC tissue for the prediction of LNM in EC based on a deep learning model [9]. This machine-learning model also achieved good performance but did not incorporate variables such as molecular classification which are becoming more widely used.

A Fully-Connected Network (FC Network) has a greater advantage in complex model fitting and distribution approximation compared with traditional statistical methods. Therefore, in this study, we used FC Network to construct a predicting model for LNM in accidentally found EC. To facilitate clinical application, we also constructed a simplified nomogram subsequently. The model constructed in this study will provide a reference for clinicians to decide on treatment for accidentally found EC after a hysterectomy.

MATERIALS AND METHODS

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Obstetrics & Gynecology Hospital of Fudan University (2020-169) and the Ethical Committee of Fudan University Shanghai Cancer Center. All the participants had been informed and signed the informed consent form.

1. Materials

Source of cases

A total of 4,400 cases of EC receiving surgical treatment from Subcenter 1 (Obstetrics & Gynecology Hospital of Fudan University) between January 2016 and February 2023 and 1,995 cases from patients attending Subcenter 2 (Fudan University Shanghai Cancer Center) between January 2013 and October 2020 were retrospectively collected. A total of 3,920 cases were included in this study based on inclusion and exclusion criteria. We also collected data prospectively from 750 EC patients receiving surgical treatment in Subcenter 1 from March 2023 to October 2023 for external validation, among which a total of 572 cases were included based on the same inclusion criteria (**Fig. 1**).

Inclusion criteria

Patients diagnosed with EC were collected. The inclusion criteria for the study were: (1) pathological diagnosis of EC by preoperative endometrial biopsy; (2) preoperative imaging (chest computed tomography [CT] and pelvic/abdomen enhanced CT/magnetic resonance imaging [MRI]) suggesting tumor confinement to the uterine body, without evidence of extrauterine involvement; (3) comprehensive staging surgery performed, including total hysterectomy + bilateral salpingectomy +/− bilateral oophorectomy + pelvic lymphadenectomy or sentinel lymph node biopsy +/− para-aortic lymphadenectomy or biopsy +/− omentectomy.

The exclusion criteria for the study were: (1) patients with a combination of other genital malignancies, such as cervical cancer; (2) patients without imaging evaluation; (3) patients with conservative treatment for more than 3 months; (4) received preoperative adjuvant chemotherapy or radiotherapy.

2. Data collection

General information

The general information includes the age at diagnosis, height, weight, body mass index, menstrual status (menopausal or not), and complications including diabetes or hypertension.

Laboratory tests

Preoperative results of the following laboratory tests were collected: fasting plasma glucose, glycated hemoglobin, serum estradiol, progesterone, testosterone, follicle-stimulating hormone, luteinizing hormone, sex hormone-binding globulin, triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein, apolipoprotein A, apolipoprotein B, alkaline phosphatase, carbohydrate antigen-125 (CA125), human epididymis protein 4.

Preoperative ultrasound

Preoperative ultrasound findings refer to the size of lesions (the largest diameter), the thickness of the endometrium (single layer), and myometrial invasion.

Pathological results

Post-operative pathological results were collected, including: post-operative pathological diagnosis, grade, depth of myometrial infiltration (classified as no, <50%, ≥50%), the degree of cervical involvement (classified as no, mucinous involvement, stromal infiltration), lymphovascular space invasion (LVSI, classified as no LVSI, focal LVSI which is <4 LVSI, and

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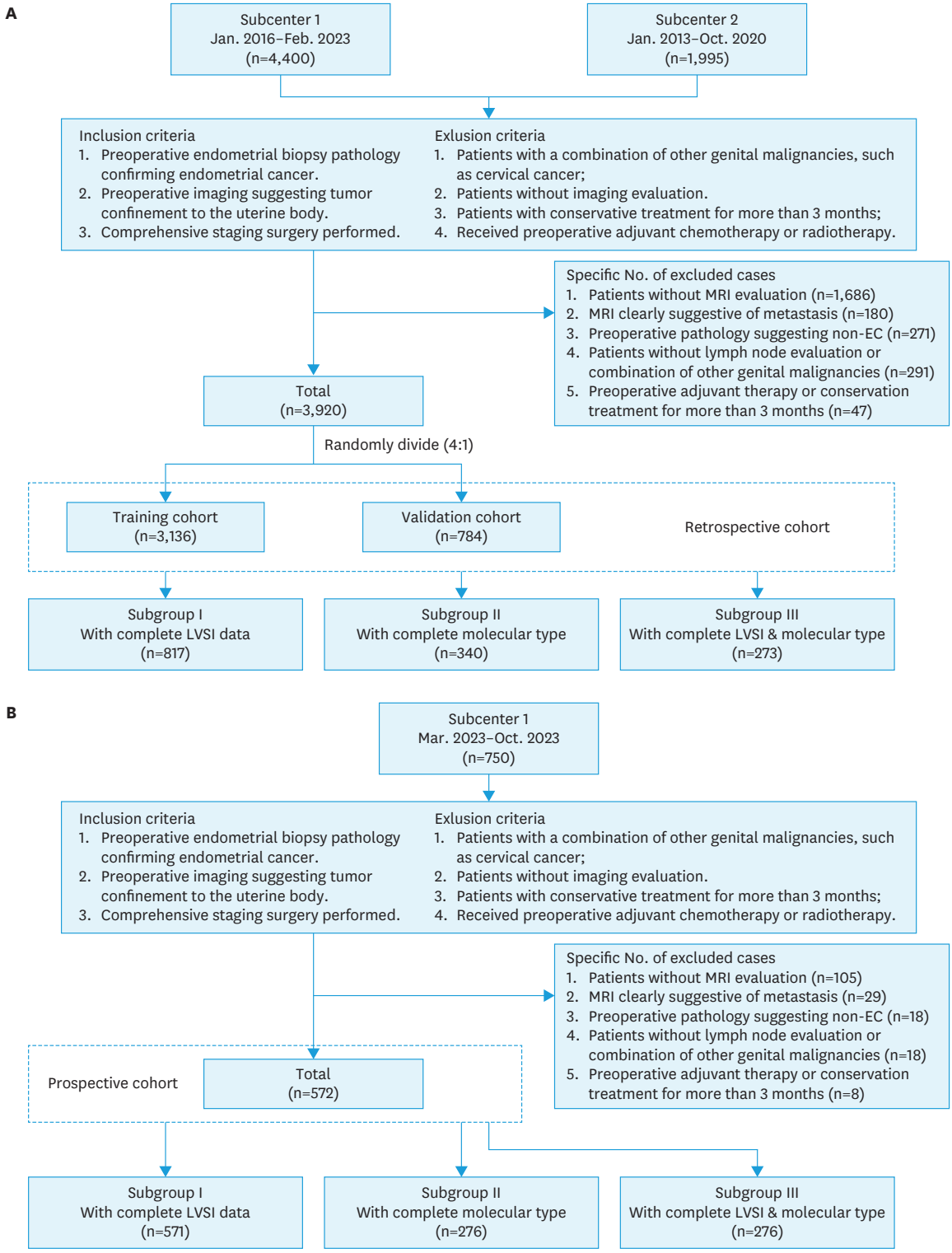

Fig. 1. Inclusion and exclusion criteria of the cohorts.
(A) Each 4,400 and 1,995 cases were retrospectively collected from subcenter 1 (the Obstetrics and Gynecology Hospital of Fudan University) and subcenter 2 (the Cancer Hospital of Fudan University). The final number of included cases was 3,920. Cases were randomly divided into the training cohort and internal validation cohort. Three hundred and forty cases of those with complete molecular type data were extracted for the subgroup. (B) Seven hundred and fifty cases from subcenter 1 (the Obstetrics and Gynecology Hospital of Fudan University) were prospectively collected for external validation. The final number of included cases was 572. Two hundred seventy-six cases of those with complete molecular type data were extracted for the subgroup.
EC, endometrial cancer; LVSI, lymphovascular space invasion; MRI, magnetic resonance imaging.

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substantial LVSI defined as the number of involved lymphovascular spaces ≥4 in at least one section [10]), microcystic elongated and fragmented (MELF), adnexal involvement, vagina involvement, mismatch repair (MMR) status (classified as dMMR or pMMR based on immunohistochemistry [11]), P53 (wild type/mutant based on immunohistochemistry), PTEN (negative/positive on immunohistochemistry), estrogen receptor (ER, classified as ≤1%, 1%–10%, >10% according to the percentage of positive-stained cells), progesterone receptor (PR, classified as ≤1%, 1%–10%, >10% according to the percentage of positive-stained cells), and Ki67 (recorded as the percentage of positive-stained cells). Next-generation sequencing technology is used for molecular classification and the results are recorded as *POLE* hypermutant, dMMR type, NSMP type, and TP53 mutant [12].

3. Model development

Selection and coding of variables

A total of 43 factors that can be retrieved in cases with incidentally found EC after a simple hysterectomy that may affect LNM were included as variables in the model. Continuous-valued variables were used directly as inputs to the model. For discrete values, one-hot coding was used.

Missing data filling methods

Due to the long period of the cases, some of the data of the cases were incomplete. Thus, we selected and verified 5 commonly used methods for handling missing data: mean, median, plurality, fixed constant, and K-nearest neighbor (KNN).

Construction and estimation of the model

An FC Network was designed for the postoperative factors in our study, and the dimensions of the input features after coding were 96. The model consists of an input layer, 4 intermediate layers (hidden layers), a dropout layer, and an output layer. The input layer of the model accepts a feature vector of size the dimension of the input feature and maps it to a hidden layer of size 256, which means the layer has 256 neurons (each connected to each of the input features). Subsequently, the intermediate layers of the model accept features from the previous layer and map them to hidden layers of sizes 128, 64, and 20, respectively. To prevent the model from overfitting, the network adds a dropout layer (Dropout) after these former layers. During training, the Dropout layer randomly sets the output of a portion of the neurons to zero to reduce the complexity of the model. The model was trained using a Dropout rate of 0.5, which indicates that half of the neurons are discarded. Finally, the output layer of the model is used to perform the binary classification task. It maps the 20 features from the fourth layer to an output of size 2. This layer uses a SoftMax activation function to calculate a probability distribution for each category. Schematic is shown in **Fig. S1**. The weights of each variable were calculated by 3 approaches: gradient and standard deviation scaling, gradient mapping to factor weights, and mean substitution. Approach 1 (gradient and standard deviation scaling): calculate the gradient of the model output to the input, a large gradient indicates that the input features of this dimension have a large impact on the output results, and then according to the standard deviation of the input features in each dimension to do the overall scaling. Approach 2 (gradient mapping to factor weights): the gradient of the model output to the input is also calculated, and then the input features are mapped back to specific factors, if a factor involves features in more than one dimension, the weights of all the features are summed up. Approach 3 (mean substitution): a factor of the input is overwritten with a mean value, similar to removing this factor. Calculate the difference between the output probability and the output probability using all the factors (take the absolute value), the larger the difference the greater the impact of this factor on the prediction result.

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The network was trained using the cross-entropy loss, defined as

$$Loss = CrossEntropy(LNM_{pred}, LNM_{label})$$

where LNM_{label} represents the actual LNM and LNM_{pred} represents the predicted LNM. The network is trained end-to-end to optimize the whole model.

In addition to FC Network, we explored several traditional machine-learning methods for comparing the performance of FC Network, including Entropy Decision Tree, Regression Decision Tree, Gaussian Plain Bayes, Polynomial Plain Bayes, Bernoulli Plain Bayes, K Nearest Neighbors, Logistic Regression, Support Vector Machines, and Random Forest.

This study measures 3 metrics of the model: precision, sensitivity, and overall accuracy [13]. A machine with Nvidia GTX 2080Ti GPU (Nvidia, Santa Clara, CA, USA) was used for the experiments. The network framework was implemented based on PyTorch. The network training was optimized using Adam optimizer with a learning rate set to 0.0001. To reduce overfitting, the weight decay factor was set to 0.0001.

According to the clinical application, LNM was not easy to detect. Therefore, our study considered the probability of less than 5% as low risk, 5% to 25% as medium risk, and more than 25% as high risk [14]. Subsequently, the model will consider "metastatic" with a predicted probability greater than 5%.

Construction of nomogram

For ease of clinical use, we combined logistic regression analysis and FC Network to construct a simplified nomogram. First, single-factor and multi-factor logistic regression analyses were performed, and those variables with statistical significance were selected. Then we chose the remaining variables which were also the top 10 weighted variables in the FC Network to construct the nomogram.

4. Statistical analysis

Differences between cohorts were assessed by t-test (normal distribution), Mann-Whitney test (not normal distribution) in continuous variables, or χ^2 test (categorical variables). The area under the curve (AUC) values of each model were compared by Delong test. Univariate and multivariate regression analyses were conducted by using SPSS Statistics (version 29.0.1.0; manufactured by International Business Machines Corporation, Armonk, NY, USA). R (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria) was used for nomogram visualization. Statistical significance was set at $p<0.05$ (2-tailed).

RESULTS

1. Clinical characteristics of retrospective cohort and prospective cohort

We eventually included 3,920 patients as a retrospective cohort. The patients were randomly grouped into training (3,136 patients) and validation (784 patients) cohorts. Another set of 572 patients were included in the prospective cohort as external validation according to the same criteria. We summarized the detailed characteristics of the 3 sets of patients in **Table 1**. Most of the clinical characteristics were not statistically significant between the training and validation cohorts, except for vagina involvement, which may be due to the small number

of positive cases. Due to the long period, some of the data were missing. The number and proportion of missing data were recorded in **Table S1**.

Table 1. Clinical characteristics of retrospective cohort and prospective cohort

Characteristics	Training cohort (n=3,136)	Validation cohort (n=784)	p	Prospective cohort (n=572)
General information				
Age (yr)	54.00 (49.00–60.00)	54.00 (49.00–60.00)	0.748	54.00 (48.00–59.00)
Height (m)	1.60 (1.56–1.63)	1.60 (1.57–1.63)	0.352	1.60 (1.57–1.63)
Weight (kg)	61.00 (55.00–69.00)	62.00 (55.88–68.60)	0.720	62.00 (55.58–70.00)
BMI (kg/m^2)	24.24 (22.03–27.05)	24.24 (22.17–26.62)	0.991	24.54 (22.16–27.30)
Menopause			0.414	
No	864 (27.55)	204 (26.02)		236 (41.26)
Yes	2,272 (72.45)	580 (73.98)		336 (58.74)
Hypertension			0.247	
No	2,175 (69.36)	561 (71.56)		417 (72.90)
Yes	961 (30.64)	223 (28.44)		155 (27.10)
Diabetes			0.957	
No	2,688 (85.71)	671 (85.59)		476 (83.22)
Yes	448 (14.29)	113 (14.41)		96 (16.78)
Laboratory tests				
FPG (mmol/L)	5.40 (5.00–5.90)	5.40 (5.00–6.00)	0.761	5.20 (4.80–5.60)
HbA1c (%)	5.70 (5.40–6.10)	5.70 (5.40–6.10)	0.759	5.70 (5.40–6.10)
E2 (pg/mL)	102.76 (51.38–238.55)	99.09 (55.05–215.00)	0.593	68.00 (37.00–209.00)
P (ng/mL)	1.21 (0.70–1.96)	1.14 (0.67–1.87)	0.610	0.76 (0.33–1.36)
T (ng/mL)	1.25 (0.83–1.77)	1.37 (0.82–1.90)	0.216	1.05 (0.56–1.53)
FSH (mIU/mL)	36.96 (7.75–70.85)	42.19 (7.77–72.70)	0.802	31.98 (6.01–65.43)
LH (mIU/mL)	16.54 (5.83–29.52)	19.54 (8.21–29.06)	0.152	14.64 (4.88–28.72)
SHBG (nmol/L)	44.20 (30.45–65.90)	44.00 (28.83–63.85)	0.570	41.80 (28.50–68.00)
TG (mmol/L)	1.52 (1.07–2.18)	1.56 (1.09–2.19)	0.358	1.33 (0.94–1.96)
TC (mmol/L)	5.15 (4.51–5.82)	5.13 (4.51–5.81)	0.970	4.79 (4.12–5.49)
HDL (mmol/L)	1.27 (1.09–1.47)	1.24 (1.06–1.46)	0.275	1.26 (1.06–1.49)
LDL (mmol/L)	3.28 (2.77–3.84)	3.22 (2.83–3.88)	0.816	3.05 (2.47–3.61)
ApoA (g/L)	1.38 (1.14–1.57)	1.36 (1.13–1.57)	0.505	1.36 (1.25–1.49)
ApoB (g/L)	0.99 (0.85–1.15)	0.99 (0.87–1.17)	0.330	0.92 (0.78–1.05)
ALP (U/L)	78.00 (63.52–95.38)	77.00 (63.00–94.00)	0.356	77.00 (63.25–90.00)
CA125 (U/mL)	17.80 (12.46–27.19)	17.46 (12.58–26.47)	0.814	16.20 (11.43–25.40)
HE4 (pmol/L)	60.05 (48.48–81.90)	59.30 (49.40–79.38)	0.853	59.30 (48.10–79.50)
Ultrasound				
Thickness of endometrium (mm)	6.00 (2.00–10.00)	6.00 (2.00–11.00)	0.555	5.00 (2.00–10.00)
Tumor size (cm)			0.463	
<2	447 (14.25)	118 (15.05)		418 (73.08)
≥2	647 (20.63)	153 (19.52)		132 (23.08)
Myometrial invasion			0.637	
Distinct boundary	1,702 (54.27)	410 (52.30)		427 (74.65)
Indistinct boundary	460 (14.67)	111 (14.16)		113 (19.76)
Myometrial infiltration	54 (1.72)	17 (2.17)		6 (1.05)
Pathological results				
Postoperative pathological type			0.705	
Endometrioid	2,837 (90.47)	706 (90.05)		512 (89.51)
Serous	115 (3.67)	31 (3.95)		24 (4.20)
Mixed	68 (2.17)	13 (1.66)		6 (1.05)
Clear cell	40 (1.28)	14 (1.79)		8 (1.40)
Others	76 (2.42)	20 (2.55)		22 (3.85)
Grade			0.812	
G1	1,784 (56.89)	437 (55.74)		370 (64.69)
G2	706 (22.51)	184 (23.47)		68 (11.89)
G3	347 (11.07)	85 (10.84)		74 (12.94)

(continued to the next page)

Table 1. (Continued) Clinical characteristics of retrospective cohort and prospective cohort

Characteristics	Training cohort (n=3,136)	Validation cohort (n=784)	p	Prospective cohort (n=572)
Myometrial invasion			0.475	
≥1/2	609 (19.42)	160 (20.41)		101 (17.66)
<1/2	2,200 (70.15)	553 (70.54)		347 (60.66)
No	327 (10.43)	71 (9.06)		124 (21.68)
LVSI			0.474	
Yes	654 (20.57)	172 (21.94)		146 (25.53)
Focal	104 (15.90)	32 (18.61)		77 (52.74)
Substantial	166 (25.38)	45 (26.16)		69 (47.26)
No	2,425 (77.33)	431 (54.97)		425 (74.30)
Cervical involvement			0.494	
Stromal involvement	115 (3.67)	27 (3.44)		55 (9.62)
Mucous involvement	308 (9.82)	88 (11.22)		16 (2.80)
No	2,713 (86.51)	669 (85.33)		501 (87.59)
Adnexa involvement			0.695	
Yes	120 (3.83)	33 (4.21)		13 (2.27)
No	3,016 (96.17)	751 (95.79)		559 (97.73)
Vagina involvement			0.002	
Yes	6 (0.19)	7 (0.89)		0 (0.00)
No	3,130 (99.81)	777 (99.11)		572 (100.00)
Parametrium involvement			0.953	
Yes	15 (0.48)	3 (0.38)		0 (0.00)
No	3,121 (99.52)	781 (99.62)		572 (100.00)
MELF			0.120	
Yes	208 (6.63)	65 (8.29)		61 (10.66)
No	2,928 (93.37)	719 (91.71)		511 (89.34)
MMR			0.426	
dMMR	690 (22.00)	183 (23.34)		144 (25.17)
pMMR	1,937 (61.77)	473 (60.33)		392 (68.53)
P53			0.981	
Wild type	2,406 (76.72)	603 (76.91)		459 (80.24)
Mutant type	333 (10.62)	83 (10.59)		81 (14.16)
PTEN			0.956	
Negative	1,535 (48.95)	378 (48.21)		368 (64.34)
Positive	812 (25.89)	202 (25.77)		165 (28.85)
Molecular type			0.326	
POLEmut	34 (1.08)	5 (0.64)		43 (7.52)
dMMR	90 (2.87)	24 (3.06)		77 (13.46)
P53abn	61 (1.95)	9 (1.15)		41 (7.17)
NSMP	101 (3.22)	16 (2.04)		115 (20.10)
ER			0.625	
≤1%	181 (5.77)	51 (6.51)		38 (6.64)
1%–10%	370 (11.80)	86 (10.97)		17 (2.97)
>10%	2,172 (69.26)	542 (69.13)		484 (84.62)
PR			0.721	
≤1%	401 (12.79)	104 (13.27)		62 (10.84)
1%–10%	620 (19.77)	163 (20.79)		38 (6.64)
>10%	1,703 (54.30)	415 (52.93)		439 (76.75)
Ki67 (%)	0.40 (0.20–0.60)	0.40 (0.20–0.60)	0.939	0.30 (0.20–0.50)
Lymph node metastasis			0.987	
Yes	218 (6.95)	55 (7.02)		30 (5.24)
No	2,918 (93.05)	729 (92.98)		542 (94.76)

Values are presented as number (%) or number (range). The p-value showed the statistical analysis between training cohort and validation cohort. For variables conforming to normal distribution, t-test was used. For continuous variables that did not conform to normal distribution, Mann-Whitney test was used. And for categorical variables, the χ^2 test was used. Statistical significance was set at $p<0.05$ (2-tailed).

ALP, alkaline phosphatase; ApoA, apolipoprotein A; BMI, body mass index; CA125, carbohydrate antigen-125; dMMR, deficient mismatch repair; E2, serum estradiol; ER, estrogen receptor; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HE4, human epididymis protein 4; LDL, low-density lipoprotein; LH, luteinizing hormone; LVSI, lymphovascular space invasion; MELF, microcystic elongated and fragmented; MMR, mismatch repair; NSMP, no specific molecular profile; P, progesterone; pMMR, proficient mismatch repair; PR, progesterone receptor; SHBG, sex hormone-binding globulin; T, testosterone; TC, total cholesterol; TG, triglycerides.

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2. Construction of prediction model using FC Network with different missing value-filling approaches

The performance of the models with different missing value-filling methods was compared by precision, sensitivity, and overall accuracy (**Table S2**). For patients with incidentally-found EC, screening out all those patients with LNM as much as possible is crucial for their prognosis, and this is highly related to the sensitivity of the model. The KNN approach has the best performance compared with the other missing value-filling approaches, with a sensitivity of 0.946. Meanwhile, the feasibility of KNN was recognized by other studies [15,16]. Therefore, we used the KNN approach to fill in the missing values. The characteristics of our cohort were recorded in **Table S3** after filling in the missing values using KNN.

3. Comparison of other machine-learning methods with FC Network

We constructed other machine-learning models based on the same cohort in our study and compared the performance of these models with FC Network. The results are shown in **Table 2**. In terms of sensitivity, FC Network is the highest, with a value of 0.946, which indicates that FC Network performs best among other models. At the same time, people with definite extrauterine metastases on imaging were excluded from the cohort of this study, thus it proved that the performance of FC Network is outstanding and can be well applied to the population of patients with incidentally detected EC.

4. Evaluation of FC Network using validation cohort and prospective cohort

We evaluated the FC Network in validation and prospective cohorts. The receiver operating characteristics (ROC) curves and results are shown in **Fig. 2A**. FC Network obtained AUC values of 0.877 (95% confidence interval [CI]=0.827–0.918) and 0.840 (95% CI=0.753–0.910) in validation and prospective cohorts, respectively. The sensitivity was 0.946 and 0.833 in validation and prospective cohorts, respectively. These results also confirmed the good effectiveness of FC Network in screening patients with LNM. As mentioned above, the threshold of less than 5%, 5%–25%, and more than 25% could be used for risk stratification. Therefore, the cases in the prospective cohort could be divided into low, medium, and high risk groups, and the numbers of cases were 345, 178, and 49, respectively.

5. Impacts of LVSI and molecular classification on the model

The predictive effectiveness of LVSI and molecular classification has been confirmed by many studies [1,17-19]. Thus, we included LVSI and molecular classification during the model construction. However, the value of LVSI and molecular classification might be underestimated due to the high rate of missing data in retrospective cohort (LVSI, more than 20%; molecular classification, more than 90%). Therefore, we extracted 3 subgroups

Table 2. Comparison of different machine-learning models

Models	Sensitivity	Precision	Overall accuracy
Decision Tree Entropy	0.273	0.341	0.912
Decision Tree Regressor	0.309	0.309	0.903
Gaussian NB	0.800	0.249	0.816
Multinomial NB	0.636	0.153	0.727
Bernoulli NB	0.800	0.320	0.861
K Neighbors	0.055	0.375	0.927
Logistic Regression	0.127	0.583	0.932
SVM	0	0	0.929
Random Forest	0.055	0.750	0.932
FC Network	0.946	0.154	0.633

FC, Fully-Connected; NB, Naive Bayes; SVM, Support Vector Machine.

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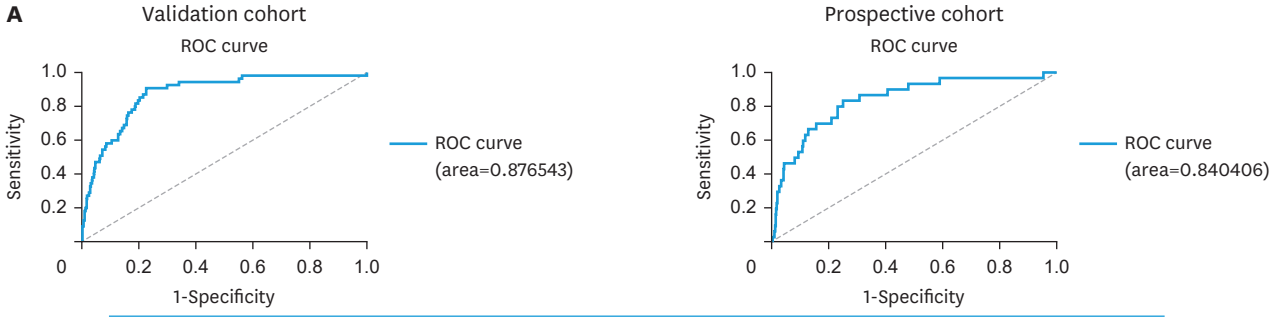
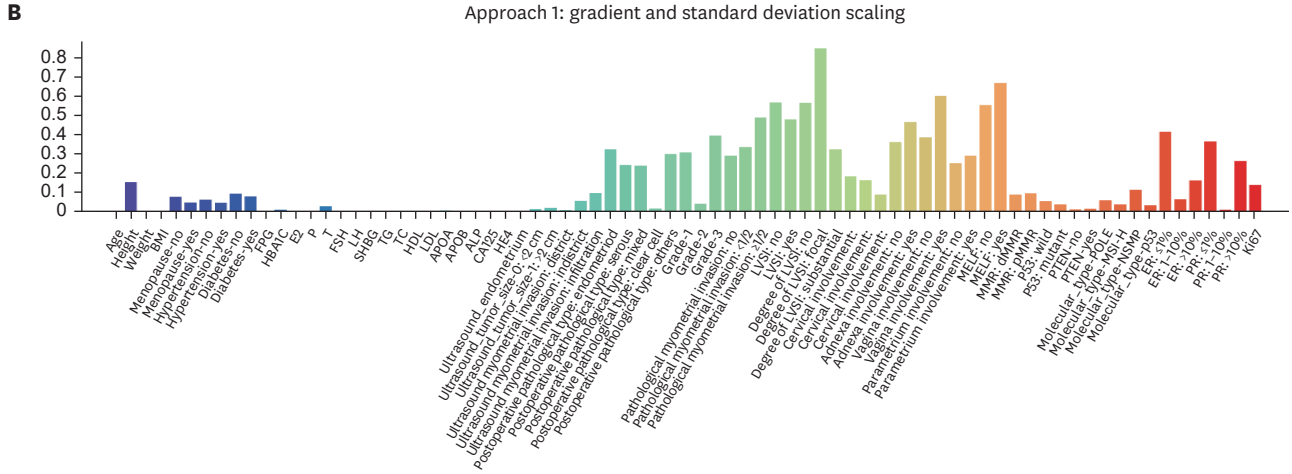


	Precision	Sensitivity	Overall accuracy	AUC
Validation cohort	0.154	0.946	0.633	0.877
Prospective cohort	0.152	0.833	0.748	0.840



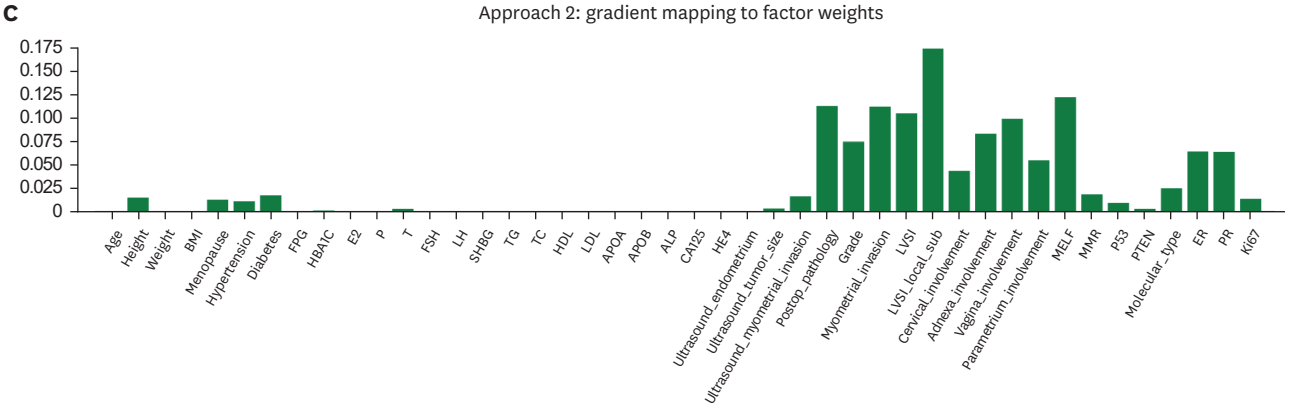


Fig. 2. The construction and estimation of Fully-Connected Network.
(A) ROC curves in internal validation and prospective external validation cohorts. (B) Approach 1: Gradient and standard deviation scaling. (C) Approach 2: Gradient mapping to factor weights. (D) Approach 3: Mean substitution.
ALP, alkaline phosphatase; ApoA, apolipoprotein A; AUC, area under the curve; BMI, body mass index; CA125, carbohydrate antigen-125; dMMR, deficient mismatch repair; E2, serum estradiol; ER, estrogen receptor; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HE4, human epididymis protein 4; LDL, low-density lipoprotein; LH, luteinizing hormone; LVSI, lymphovascular space invasion; MELF, microcystic elongated and fragmented; MMR, mismatch repair; NSMP, no specific molecular profile; P, progesterone; pMMR, proficient mismatch repair; PR, progesterone receptor; ROC, receiver operating characteristics; SHBG, sex hormone-binding globulin; T, testosterone; TC, total cholesterol; TG, triglycerides.
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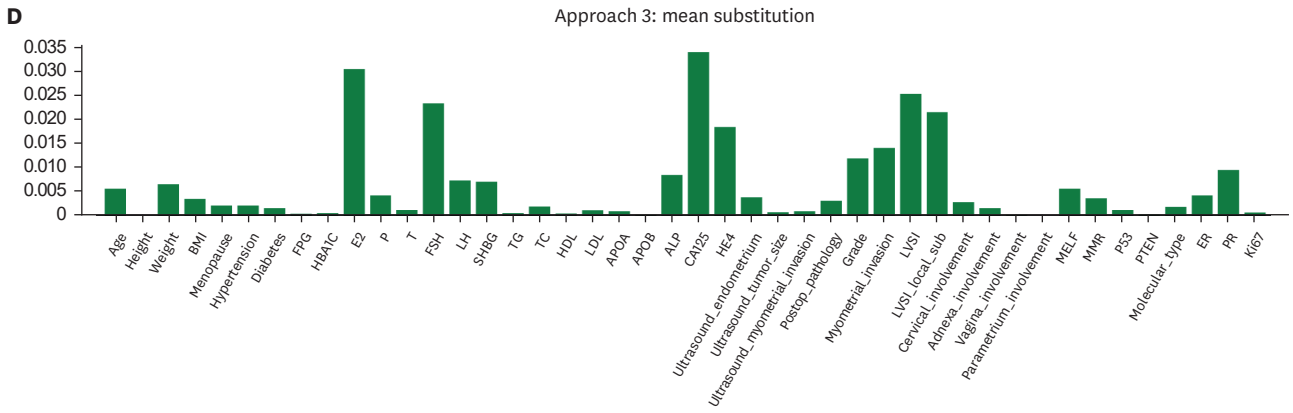

Fig. 2. (Continued) The construction and estimation of Fully-Connected Network.
(A) ROC curves in internal validation and prospective external validation cohorts. (B) Approach 1: Gradient and standard deviation scaling. (C) Approach 2: Gradient mapping to factor weights. (D) Approach 3: Mean substitution.
ALP, alkaline phosphatase; ApoA, apolipoprotein A; AUC, area under the curve; BMI, body mass index; CA125, carbohydrate antigen-125; dMMR, deficient mismatch repair; E2, serum estradiol; ER, estrogen receptor; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HE4, human epididymis protein 4; LDL, low-density lipoprotein; LH, luteinizing hormone; LVSI, lymphovascular space invasion; MELF, microcystic elongated and fragmented; MMR, mismatch repair; NSMP, no specific molecular profile; P, progesterone; pMMR, proficient mismatch repair; PR, progesterone receptor; ROC, receiver operating characteristics; SHBG, sex hormone-binding globulin; T, testosterone; TC, total cholesterol; TG, triglycerides.

from retrospective and prospective cohorts to further investigate the impacts of LVSI and molecular classification on FC Network. The 3 subgroups were: subgroup I, patients with complete LVSI data (retrospective, n=817; prospective, n=571); subgroup II, patients with complete molecular classification data (retrospective, n=340; prospective, n=276); subgroup III patients with complete LVSI and molecular classification data (retrospective, n=273; prospective, n=276). The missing values of the rest variables were filled in using the KNN approach in the 3 subgroups. We constructed different models using these 3 subgroups for the subsequent analyses.

In subgroup I, the model incorporating LVSI had a trend of lower sensitivity (0.500 vs. 0.625 in validation cohort, p=0.484; 0.500 vs. 0.767 in prospective cohort, p=0.392) compared to the model without LVSI. In subgroup II, the model incorporating molecular classification had a trend of higher sensitivity (both were 1 in validation cohort, p=0.875; and 1 vs. 0.963 in prospective cohort, p=0.789). In subgroup III, the model incorporating LVSI & molecular classification had a trend of higher sensitivity than the other (both were 1 in validation cohort, p=0.391 and 0.955 vs. 0.591 in prospective cohort, p=0.445) (**Table S4**).

6. Construction of the simplified nomogram

To construct a simplified nomogram, we performed univariate and multivariate regression analysis in training cohort to verify the correlation between 43 variables and LNM (**Tables S5** and **S6**). The following factors remained independent risk factors for LNM: CA125, grade, myometrial invasion, LVSI, MELF, PR, and adnexa involvement. **Fig. 2B-D** shows the weights of 43 variables by the approach of gradient and standard deviation scaling, gradient mapping, and mean substitution, which were recorded in **Table S7**. It's worth noting that these independent factors in regression analysis were also in the top 10 weighted variables in the FC Network, which indicates the important role of these variables in affecting LNM. In clinical application, patients with incomplete staging surgery might not receive adnexectomy. LVSI and degree of LVSI have significant covariance, and we selected LVSI for further study. Therefore, the final selected variables for the construction of the nomogram were LVSI, Myometrial invasion (pathological result), MELF, PR, CA125, and grade. The best cutoff value

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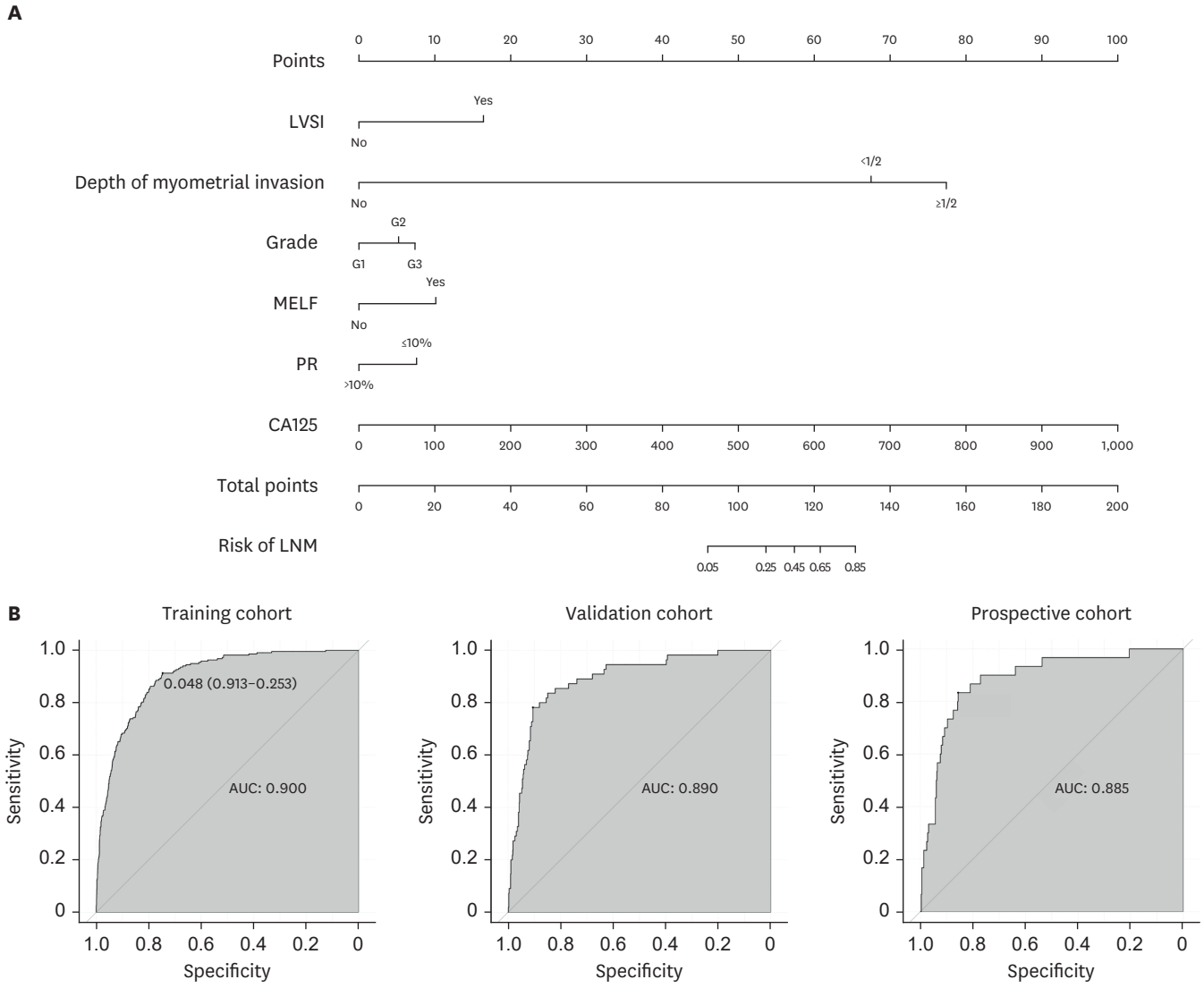

Fig. 3. Establishment and evaluation of nomogram.
(A) Nomogram for prediction of lymph node metastasis. (B) ROC curves of nomogram in the training, internal validation, and prospective external validation cohorts. CA125, carbohydrate antigen-125; LNM, lymph node metastasis; LVSI, lymphovascular space invasion; MELF, microcystic elongated and fragmented; PR, progesterone receptor; ROC, receiver operating characteristics.

was 4.8% which was similar to the FC Network. The nomogram is shown in **Fig. 3A** and the ROC curves are shown in **Fig. 3B**. The nomogram obtained AUC values of 0.890 and 0.885 in validation and prospective cohorts respectively. The points for each variable are recorded in **Table S8**.

DISCUSSION

Various predicting models have been pursued to distinguish these patients without complete surgical staging between high-risk and low-risk groups of LNM. An earlier study recommended evaluation using the laparoscopic approach for all patients with EC without complete surgical staging [20]. Another study has reported the 3 criteria: depth

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of myometrial invasion, size of the tumor, and grade for helping the treatment planning in patients with incomplete surgical staging [21]. Nevertheless, it faces difficulty in the integration of the conventional factors and other newly emerged prognostic factors such as molecular classification [22]. Also, most existing models focus on preoperative prediction of lymph node involvement, leaving a gap in risk assessment for patients accidentally diagnosed postoperatively. Indeed, the number of cases with accidentally diagnosed EC after surgery is low. However, due to the limited number of such cases, current clinical guidelines for postoperative management remain insufficiently defined for these specific patients, resulting in uncertainty in treatment decisions. Therefore, we aim to develop a specialized predictive model for LNM risk in these patients, enabling more accurate postoperative assessment and optimizing individualized treatment strategies to ultimately improve patient outcomes. In the present study, we used FC Network to construct a model for predicting LNM in clinically early-stage patients without evidence of extrauterine involvement, which can be used in accidentally found EC after hysterectomy to predict the risk of LNM. The model can help clinical decision-making on whether or not to perform lymph node dissection in these incomplete staged EC patients. Here are our recommendations based on our risk stratification: For low-risk patients (with a probability of less than 5%): regular follow-up is recommended. For medium-risk patients (with a probability of 5% to 25%): lymph node dissection could be considered to further clarify the presence of LNM. For high-risk patients (with a probability of more than 25%): lymph node dissection is highly advised to ensure thorough evaluation and management of potential LNM.

These 43 variables are derived from general information, laboratory tests, ultrasound, and pathological results to optimize a more precise prediction of the risk. As expected, our FC Network yielded good sensitivity in screening out patients with lymph node metastases. We subsequently compared the performance of FC Network to other traditional machine-learning models which indicated our model was optimal. Meanwhile, the evaluation of the FC Network was also performed in the validation and prospective cohorts. In our model, these variables: LVSI, MELF, postoperative pathological type, myometrial and vagina involvement, ER, PR, CA125, and grade were proven to be highly associated with LNM, which is consistent with other studies [23-25]. This also demonstrates the reliability of FC Network. The simplified nomogram was constructed using LVSI, myometrial invasion, tumor grade, MELF, PR, and CA125. Kang et al. [26] demonstrated that serum CA125 and MRI are effective criteria for classifying low-risk LNM in EC, achieving an AUC of 0.85. Patients meeting the following criteria were classified as low-risk: endometrioid histology, no deep myometrial invasion, no enlarged lymph nodes, no suspicious extrauterine spread, and CA125 <35 U/mL. These criteria showed a sensitivity of 0.849 and specificity of 0.555 in a cohort study [27]. The consistent inclusion of CA125 and myometrial invasion in model construction further supports the strong correlation of selected variables with LNM.

The values of LVSI and molecular classification in predicting the risk of LNM have been proven by several studies [28-31]. Considering the certain proportion of missing data in LVSI and molecular classification, we consequently explored the impacts of these 2 key factors on our model. Our results showed no statistically significant difference in the effect of incorporating or not incorporating LVSI and/or molecular type on predictive efficacy, but it seems that there is optimal sensitivity when LVSI and molecular classification are incorporated, especially in prospective cohorts that had fewer missing values. However, it still can not assert whether it's important or not of these 2 factors due to the limited cases and the same fill-in values in other variables.

Our model achieved a sensitivity of 0.946 and 0.877 of AUC which is satisfactory and useful. For clinical application, we recommend clinicians collect as many 43 factors as possible for a single patient when using our model to make predictions. Also, we proposed a simplified nomogram for easy use. The nomogram obtained AUC values of 0.890 and 0.885 in the validation and prospective cohorts which proves the possibility of use of nomogram as a substitute for FC Network in certain situations.

The highlighted findings of our study are as follows. First of all, the integration of 43 wide-range variables shows a large potential in predicting LNM. Secondly, the FC Network is superior to other traditional machine-learning models based on the same cohort in which cases with definite extrauterine lesions were excluded. Finally, the simplified nomogram provides a feasible supplement in various situations in clinical applications. However, there are some limitations in this study. First, although the scientific validity of multiple ways of filling in the missing data has been proven, the complete cohort data is irreplaceable. Second, the number of cases in the prospective cohort was small, and thus the use of a prospective cohort to validate the sensitivity of the present model to screen patients with LNM needs to be further validated by including more cases from further prospective studies. Finally, since the important role of imaging data is evolving [32], imaging data, such as MRI, can be supplemented to our model to obtain a more accurate prediction model. From a clinical perspective, physicians are more interested in preoperative prediction of LNM, as this is often a critical factor in surgical decision-making. Given the superior sensitivity of FC Networks in predicting LNM, we plan to leverage this approach to develop a preoperative risk prediction model which aims to assist clinicians in making more accurate assessments of LNM risk before surgery. We anticipate that this model will play a critical role in preoperative decision-making, optimizing treatment strategies, and ultimately improving clinical outcomes.

Overall, the FC network proposed in our study may provide clinicians with a novel and reliable reference for postoperative patients with incidentally detected EC, in addition to imaging. Stratification toward these patients based on the FC Network would help clinicians in decision-making.

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SUPPLEMENTARY MATERIALS

Table S1
The number and percentage of cases with missing data

Table S2
Comparison of different filling methods

Table S3
Clinical characteristics of retrospective cohort after fill-in using KNN

Table S4
Comparison of different models

Table S5
The p-values of single-factor logistic regression in training cohort

Table S6
The p-values of multi-factor logistic regression in training cohort

Table S7
The weights of variables in FC Network

Table S8
The risk of lymph node metastasis for different combinations of variables

Fig. S1
Schematic of Fully-Connected Network.

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