Metabolic risk score as a predictor in a nomogram for assessing myometrial invasion for endometrial cancer

YAN QIANG[1*], QINFEN ZHANG[2*] and LINGYAN DONG[1]

[1]Department of Gynecology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu 210000; [2]Department of Obstetrics and Gynecology, Zhongda Hospital, Southeast University, Nanjing, Jiangsu 210009, P.R. China

Received November 1, 2022; Accepted January 10, 2023

DOI: 10.3892/ol.2023.13700

Abstract. The purpose of the present study was to investigate the predictive value of metabolic syndrome in evaluating myometrial invasion (MI) in patients with endometrial cancer (EC). The study retrospectively included patients with EC who were diagnosed between January 2006 and December 2020 at the Department of Gynecology of Nanjing First Hospital (Nanjing, China). The metabolic risk score (MRS) was calculated using multiple metabolic indicators. Univariate and multivariate logistic regression analyses were performed to determine significant predictive factors for MI. A nomogram was then constructed based on the independent risk factors identified. A calibration curve, a receiver operating characteristic (ROC) curve and decision curve analysis (DCA) were used to evaluate the effectiveness of the nomogram. A total of 549 patients were randomly assigned to a training or validation cohort, with a 2:1 ratio. Data was then gathered on significant predictors of MI in the training cohort, including MRS [odds ratio (OR), 1.06; 95% confidence interval (CI), 1.01-1.11; P=0.023], histological type (OR, 1.98; 95% CI, 1.11-3.53; P=0.023), lymph node metastasis (OR, 3.15; 95% CI, 1.61-6.15; P<0.001) and tumor grade (grade 2: OR, 1.71; 95% CI, 1.23-2.39; P=0.002; Grade 3: OR, 2.10; 95% CI, 1.53-2.88; P<0.001). Multivariate analysis indicated that MRS was an independent risk factor for MI in both cohorts. A nomogram was generated to predict a patient's probability of MI based on the four independent risk factors. ROC curve analysis showed that, compared with the clinical model (model 1), the combined model with MRS (model 2) significantly improved the diagnostic accuracy of MI in patients with EC (area under the curve in model 1 vs. model 2: 0.737 vs. 0.828 in the training cohort and 0.713 vs. 0.759 in the validation cohort). Calibration plots showed that the training and validation cohorts were well calibrated. DCA showed that a net benefit is obtained from the application of the nomogram. Overall, the present study developed and validated a MRS-based nomogram predicting MI in patients with EC preoperatively. The establishment of this model may promote the use of precision medicine and targeted therapy in EC and has the potential to improve the prognosis of patients affected by EC.

Correspondence to: Dr Lingyan Dong, Department of Gynecology, Nanjing First Hospital, Nanjing Medical University, 68 Changle Road, Nanjing, Jiangsu 210000, P.R. China
E-mail: wzwforever@163.com

*Contributed equally

Key words: endometrial cancer, myometrial invasion, metabolic syndrome, predictive nomogram, receiver operating characteristic curve

Introduction

Endometrial cancer (EC) is one of the three most common malignant tumors of the female reproductive system, and its incidence has been increasing globally, as described by Global Disease Burden (GDB) statistics. GDB statistics have also reported that the death rate and disability-adjusted life years have been decreasing over the past 30 years due to EC (1).

There is a close association between myometrial invasion (MI) in advanced EC and a poor prognosis (2). Yet the mechanisms involved in malignant tumor invasion and metastasis are still unclear. The understanding of EC biology has progressed thanks to continuous breakthroughs in diagnosis and in treatment technologies; however, a number of aspects of treatment are still controversial, such as the use of surgery and fertility-sparing treatment.

Nomograms are graphic calculation tools that visualize and individualize prediction in different situations, and they have been used for several types of cancer, including endometrial stromal sarcoma and metastatic tumors (3,4). A number of established nomograms are available to screen lymph node metastasis (LNM), recurrence, overall survival and cancer-specific survival rates in patients with EC (5,6). Yet, to the best of our knowledge, risk prediction nomograms that correctly estimate MI are limited, and the most commonly used and validated nomogram is based on magnetic resonance imaging (MRI) (7).

Metabolic syndrome (MetS) represents a cluster of cardiovascular risk factors, including elevated blood pressure, obesity, high circulating triglyceride (TG), dysglycemia and low circulating high-density lipoprotein cholesterol (HDL-C). One study indicated that EC is a form of cancer that has

associations with metabolic diseases, and that EC incidence increases with metabolic disease prevalence (8).

Metabolic parameters can be obtained in cost-effective and non-invasive ways. Metabolic Risk Score (MRS) has recently been developed and is considered a good index to provide information on a patient's metabolic status. MRS is based on a set of markers, including pulse pressure (PP), body mass index (BMI), fasting blood glucose (FBG), TG and HDL-C. The better predictive value of MRS in comparison with the model based on traditional clinicopathological characteristics has been confirmed in a variety of tumors, such as esophageal cancer (9). MI is currently investigated and nomograms constructed based on radiological features collected with MRI (7), but the exact relationship between the MRS and MI in patients with EC has not yet been reported.

In the present study, univariate and multivariate analyses were conducted in order to reveal the risk factors for MI. A nomogram that integrates clinicopathological characteristics and MRS was subsequently developed. Internal validation was then performed based on a cohort of patients using receiver operating characteristic (ROC) and calibration curves. The aim of this study was to develop a nomogram that is useful in clinical practice to predict MI in patients with EC based on clinicopathological parameters. This would allow clinicians to screen out high-risk groups and develop appropriate treatment plans.

Materials and methods

Patients and variables selection. Data was retrospectively collected from female patients diagnosed with EC between January 2006 and December 2020 at the Department of Gynecology in Nanjing First Hospital. Patients whose pathology was confirmed as EC by histology were eligible for inclusion. The exclusion criteria were as follows: i) Combination with other malignant tumors; ii) absence of medical records; iii) a history of any preoperative therapy; and iv) patients <18 years old. After application of the strict inclusion and exclusion criteria, a total of 1,076 cases were included for further analysis. A total of 549 patients who were diagnosed with EC and underwent staging surgery were included in the final study following application of inclusion and exclusion criteria. The patients were randomly divided into a training cohort (n=366) and a validation cohort (n=183), with a 2:1 ratio. The clinical and pathological information of these patients were collected preoperatively, including age, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), PP, serum fasting blood glucose (FBG), cholesterol, TG and HDL-C levels, diabetes mellitus (DM), hypertension (HP) and menopause status, histological type, tumor grade, and presence of MI and LNM. The study cohort was examined prior to surgery with MRI to determine the presence of LNM. MI <50% or MI ≥50% was defined by the depth of MI according to their pathological characteristics, which were extracted from the pathology report. MetS was diagnosed according to diagnostic criteria proposed by the Chinese Diabetes Society in 2004 (10), and PP was calculated as the difference between SBP and DBP. As these factors of metabolic origin tend to occur together, MRS was hence generated based on baseline BMI, PP, FBG, TG and HDL-C values. In the present study, the rationales of a 'points' system and the validity of shrinkage method (11) were employed to generate MRS when all five metabolism-related factors were analyzed in quintiles. The detailed process is illustrated in Table SI.

Development and validation of the nomogram. Univariate and multivariate logistic regression analyses were used to identify independent risk factors predictive for MI. Significant factors identified in multivariate logistic regression were then included in the development of the nomogram. The performance of the nomogram was assessed in both the training and the validation group. The ROC curves of the nomogram were calculated. ROC curves reflect the accuracy and specificity of a model by calculating the area under the curve (AUC). The larger the AUC, the higher the accuracy and specificity of the model. A calibration plot was generated to visualize the association between prediction model and actual outcomes. Decision Curve Analysis (DCA) was performed to measure the clinical utility of the nomogram. A net benefit (NB) analytic measure puts benefits and drawbacks on the same scale, with the vertical axis representing the NB and the horizontal axis representing the probability threshold. The model with the highest NB at a particular threshold probability has a higher clinical value and is more beneficial in clinical practice. The performance of the MRS and other conventional clinical characteristics associated with MI in patients with EC was evaluated using univariate and multivariable logistic regression analyses. Next, an MI-associated nomogram with independent risk factors was performed with the 'rms' and 'Hmisc' R packages. The ROC, NB and DCA curve of the prediction model were then analyzed by Empower-Stats software (X&Y Solutions, Inc.) in both cohorts.

Statistical analysis. Categorical variables are expressed as n (%) and continuous variables are expressed as the mean ± standard deviation. The χ^2 or Fisher's exact tests were applied for categorical variables. Student's t-test was applied for continuous variables. Univariable and multivariate logistic analyses were used to evaluate the associations between the risk of MI and clinicopathological parameters in patients with EC. Statistical analyses were conducted using SPSS version 26.0 software (IBM Corp.), the statistical software package R (http://www.R-project.org; The R Foundation) and Empower-Stats. The 'Random Number Generators' function of SPSS software was used to randomly group the patients. Unless otherwise indicated, all tests were two-sided and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of patients. As shown in Table I, a total of 549 patients were included in the study. Among these, 366 were enrolled in the training cohort, and 183 in the validation cohort. The mean ages of the patients within the training and validation sets were 55.96±9.76 and 55.81±9.12 years (age range, 20-75 years). The MRS was 2.64±4.40 and 2.54±4.14 in the training and validation sets, respectively. In the training set, MI ≥50% accounted for 22.13% of the group, while in the validation set, the proportion was 25.68%. DM (23.33% in the training cohort and 25.14% in the validation cohort) and HP

Table I. Basic characteristics of study participants (n=549) in the training and validation groups.

Characteristic	Training	Validation	P-value
Patients, n	366	183	
Age, years	55.96±9.76	55.81±9.12	0.929
BMI, kg/m^2	26.18±4.41	26.30±4.71	0.743
SBP, mmHg	125.88±14.30	128.64±16.99	0.138
DBP, mmHg	78.08±8.51	79.99±9.88	0.049
PP, mmHg	47.80±12.54	48.66±12.39	0.370
FBG, mmol/l	6.03±1.69	5.89±1.53	0.287
TG, mmol/l	1.63±1.09	1.56±0.81	0.734
HDL-C, mmol/l	1.21±0.30	1.23±0.41	0.675
CA125, U/ml	61.90±277.16	110.04±500.84	0.341
MRS	2.64±4.40	2.54±4.14	0.669
MI, n (%)			0.353
<50%	285 (77.87)	136 (74.32)	
≥50%	81 (22.13)	47 (25.68)	
Menopausal status, n (%)			0.850
Pre-	131 (35.79)	64 (34.97)	
Post-	235 (64.21)	119 (65.03)	
DM, n (%)			0.620
No	281 (76.78)	137 (74.86)	
Yes	85 (23.22)	46 (25.14)	
HP, n (%)			0.619
No	230 (62.84)	111 (60.66)	
Yes	136 (37.16)	72 (39.34)	
Histological type, n (%)			1.000
EEA	326 (89.07)	163 (89.07)	
Others	40 (10.93)	20 (10.93)	
LNM, n (%)			0.586
Negative	337 (92.08)	166 (90.71)	
Positive	29 (7.92%)	17 (9.29)	
Grade, n (%)			0.431
G1	125 (34.15)	69 (37.70)	
G2	156 (42.62)	80 (43.72)	
G3	85 (23.22)	34 (18.58)	

Data are presented as the mean ± standard deviation unless otherwise specified. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; FBG, serum fasting blood glucose; TG, triglyceride; HDL-C, high-density lipoprotein; DM, diabetes mellitus; HP, hypertension; MRS, metabolic risk score; MI, myometrial invasion; LNM, lymph node metastasis.

[136 patients (37.16%) in the training cohort and 72 patients (39.34%) in the validation cohort] were included in the study. Endometrioid endometrial carcinoma (EEA) histological type was present in 89.07% of patients for both groups, with other types including serous carcinoma and a mixed type, among others. Most patients (92.08 and 90.71% for the training and validation sets, respectively) were negative for LNM. In terms

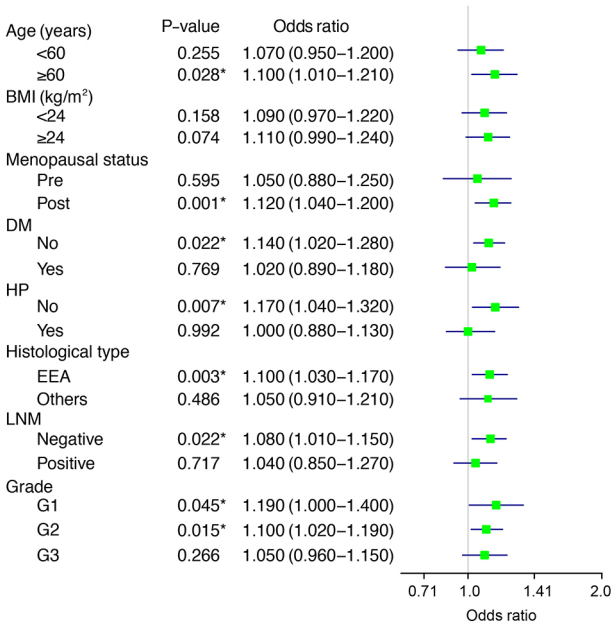

Figure 1. Stratified analysis between metabolic risk score and myometrial invasion for different clinicopathological characteristics. BMI, body mass index; DM, diabetes mellitus; HP, hypertension; LNM, lymph node metastasis; EEA, endometrioid endometrial carcinoma.

of tumor grade, in the training group 125 (34.15%) patients had a low tumor grade (G3), 156 (42.62%) patients had a moderate tumor grade (G2) and 85 (23.22%) patients had a high tumor grade (G1). The values were close for both groups. There were no significant differences between the two cohorts for any clinicopathological feature (P<0.05).

Univariate and multivariate analyses for MI. The univariate analysis considered age, BMI, SBP, DBP, PP, FBG, TG, HDL-C, cancer antigen 125, MRS, menopause status, DM, HP, histological type, LNM and tumor grade as potential risk factors for MI. Both the training and the validation cohorts indicated that MRS (training set: OR, 1.06; 95% CI, 1.01-1.11; P=0.023; validation set: OR, 1.08; 95% CI, 1.02-1.14; P=0.013), histological type (training set: OR, 1.98; 95% CI, 1.11-3.53; P=0.023; validation set: OR, 2.16; 95% CI, 1.07-4.36; P=0.032), LNM (training set: OR, 3.15; 95% CI, 1.61-6.15; P<0.001; validation set: OR, 4.72; 95% CI, 1.99-11.17; P<0.001), and tumor grade (training set: Grade 2; OR, 1.71; 95% CI, 1.23-2.39; P=0.002; grade 3; OR, 2.10; 95% CI, 1.53-2.88; P<0.001; validation set: grade 2; OR, 1.64; 95% CI, 1.24-2.18; P<0.001; grade 3, OR, 2.07; 95% CI, 1.39-3.07; P<0.001) were risk factors for MI. Detailed information is listed in Table II. Next, stratified analyses were conducted to reveal whether the influence of MRS on MI was stable in different clinicopathological features. Fig. 1 shows that the effect was more obvious in patients ≥60 years, with postmenopausal status, with no DM or HP, with an EEA histology, no LNM, and tumor grade 1 and 2. It can be concluded that MRS is closely related with MI, and that it can increase the risk of MI in patients with EC.

Development and validation of nomogram. Based on the risk factors identified in the univariate and multivariate regression analyses, a nomogram was designed to predict MI in patients

Table II. Univariate analysis for myometrial invasion in patients with endometrial cancer.

	Training set				Validation set			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Parameter	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, years	1.06 (1.03-1.08)	<0.001	1.02 (0.98-1.05)	0.253	1.05 (1.02-1.09)	0.039	1.11 (0.98-1.05)	0.396
BMI, kg/m^2	0.99 (0.94-1.04)	0.691			0.95 (0.88-1.02)	0.159		
SBP, mmHg	1.02 (1.00-1.03)	0.055			1.01 (0.99-1.02)	0.490		
DBP, mmHg	0.99 (0.97-1.02)	0.446			0.99 (0.96-1.02)	0.689		
PP, mmHg	1.02 (1.01-1.04)	0.006			1.02 (0.99-1.04)	0.180		
FBG, mmol/l	1.13 (1.00-1.28)	0.056			1.13 (0.95-1.34)	0.165		
TG, mmol/l	0.88 (0.67-1.14)	0.316			0.80 (0.53-1.20)	0.275		
HDL-C, mmol/l	0.64 (0.29-1.39)	0.258			0.57 (0.23-1.41)	0.225		
CA125, U/ml	1.00 (1.00-1.00)	0.357			1.00 (1.00-1.00)	0.087		
MRS	1.10 (1.04-1.16)	0.014	1.06 (1.01-1.11)	0.023	1.09 (1.01-1.18)	0.004	1.08 (1.02-1.14)	0.013
Menopausal status								
Pre-	1.00		1.00		1.00		1.00	
Post-	2.29 (1.36-3.85)	0.019	1.32 (0.71-2.47)	0.381	2.64 (1.27-5.49)	0.001	1.41 (0.65-3.09)	0.384
DM								
No	1.00				1.00			
Yes	0.93 (0.54-1.59)	0.789			1.22 (0.61-2.45)	0.569		
HP								
No	1.00				1.00			
Yes	1.42 (0.91-2.22)	0.127			1.17 (0.62-2.19)	0.630		
Histological type								
EEA	1.00		1.00		1.00		1.00	
Others	2.33 (1.19-4.56)	0.014	1.98 (1.11-3.53)	0.023	2.59 (1.03-6.55)	0.044	2.16 (1.07-4.36)	0.032
LNM								
Negative	1.00		1.00		1.00		1.00	
Positive	5.53 (2.78-11.03)	<0.001	3.15 (1.61-6.15)	<0.001	2.85 (1.11-7.30)	0.029	4.72 (1.99-11.17)	<0.001
Tumor grade								
G1	1.00		1.00		1.00		1.00	
G2	3.70 (1.99-6.90)	<0.001	1.71 (1.23-2.39)	0.002	2.85 (1.25-6.51)	0.013	1.64 (1.24-2.18)	<0.001
G3	5.04 (2.56-9.91)	<0.001	2.10 (1.53-2.88)	<0.001	6.76 (2.65-17.25)	<0.001	2.07 (1.39-3.07)	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; FBG, serum fasting blood glucose; TG, triglyceride; HDL-C, high-density lipoprotein; DM, diabetes mellitus; HP, hypertension; MRS, metabolic risk score; LNM, lymph node metastasis.

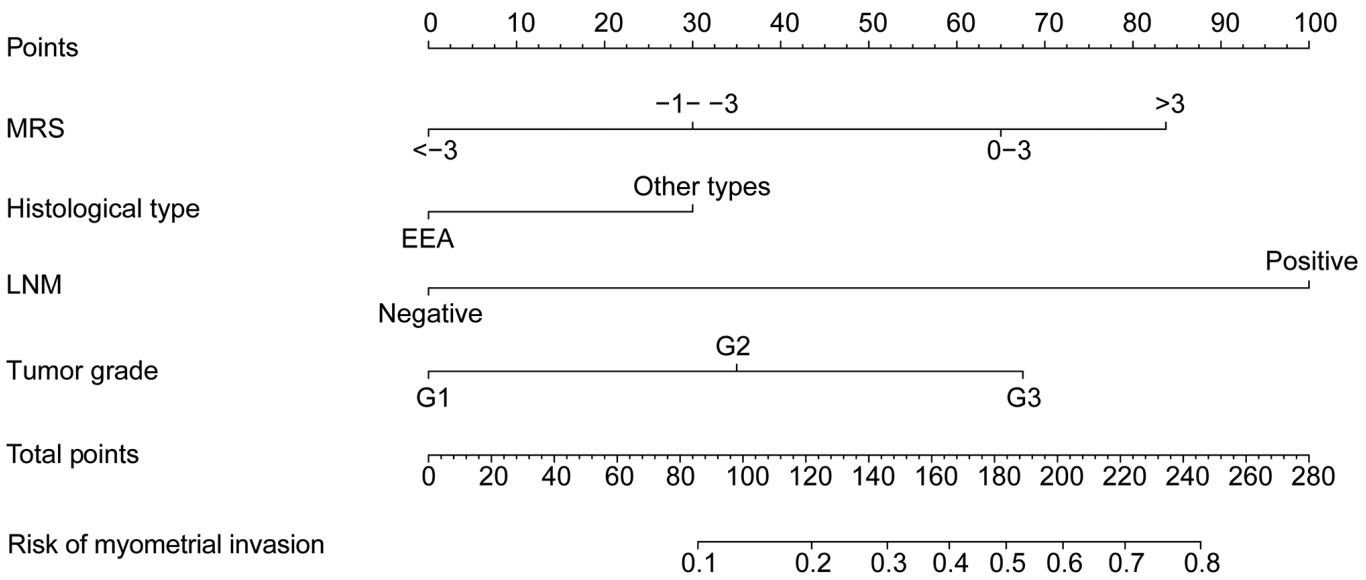

Figure 2. Nomogram predicting myometrial invasion in patients with endometrial cancer. MRS, metabolic risk score; EEA, endometrioid endometrial carcinoma; LNM, lymph node metastasis.

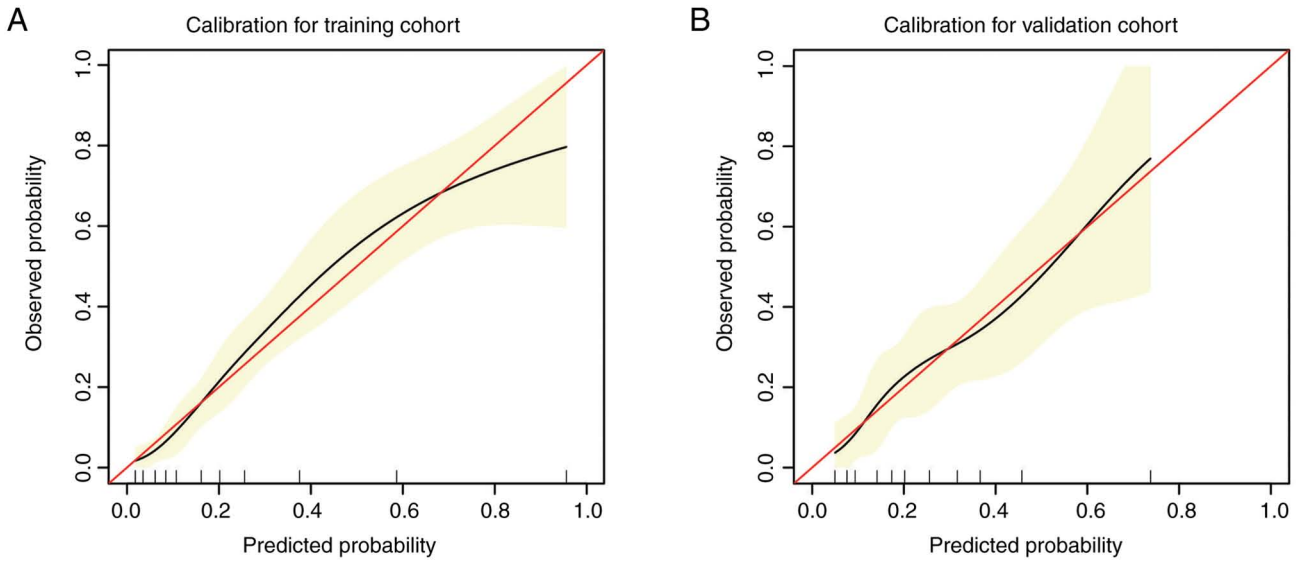

Figure 3. Calibrations of the nomogram in the (A) training and (B) validation cohorts.

with EC (Fig. 2). From the nomogram, it was observed that LNM has the greatest influence on MI, followed by MRS and other risk factors. The highest total score was 280 points, and the accumulated score for each variable state represents the probability of MI. Discrimination and calibration analyses were applied to assess the performance of the final model. The results revealed that the nomogram was well calibrated for predicting MI both in the training cohort and in the validation cohort (Fig. 3A and B).

To further investigate the value of MRS in the prediction of MI for patients with EC, two models were created. Model 1 included the clinical variables of histological type, LNM and tumor grade. Model 2 included the variables of model 1 and MRS. The nomogram had an AUC value of 0.828 for model 2 in the training group, compared with 0.737 for model 1 ($P<0.05$; Fig. 4A). In the validation group, the AUC value was 0.795 for model 2 and 0.713 for model 1 ($P<0.05$; Fig. 4B). The accuracy of the nomogram was also validated in the total cohort, and the results indicated that the AUC value was 0.806 for model 2 and 0.757 for the model 1 ($P<0.05$; Fig. S1A). To further evaluate the clinical benefit of MRS performance in the nomogram, DCA was conducted, which showed the benefits achieved with the application of the nomogram. The NB in patients with EC is significantly reduced when MRS is removed from the model, in both of the sets (Fig. 5A and B). The NB in model 2 also achieved a higher value than that in model 1 in the whole cohort (Fig. S1B).

Discussion

EC is a frequently occurring gynecological malignancy with a high OS rate, especially when diagnosed at an early stage.

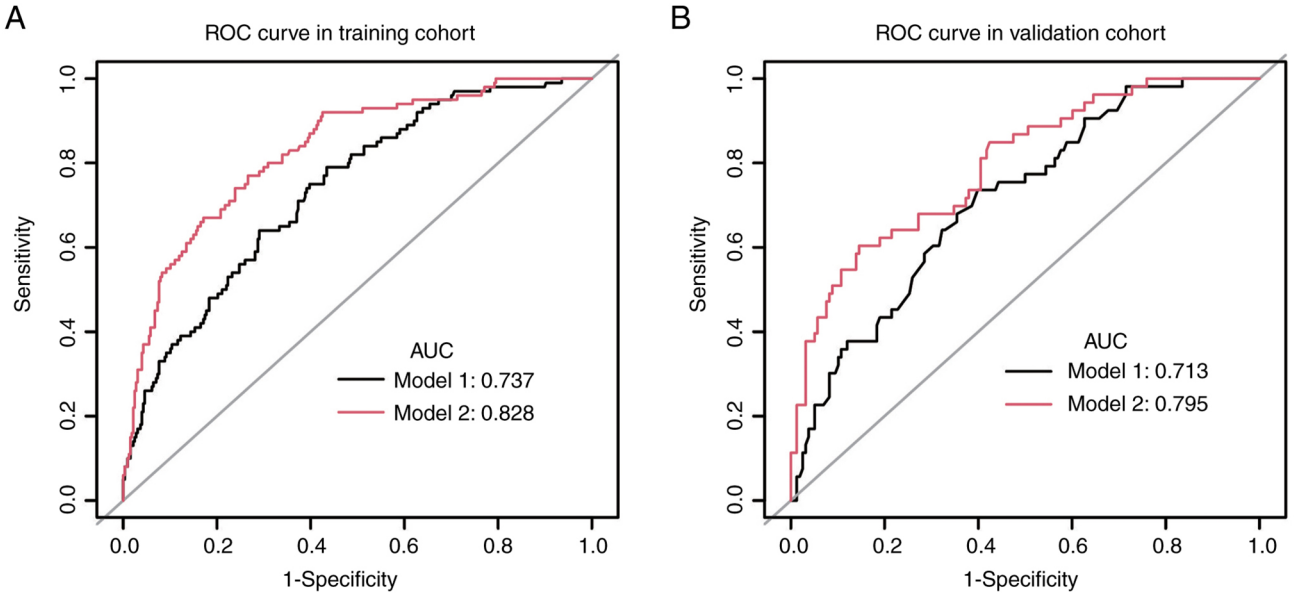

Figure 4. Predictive accuracy evaluated by AUC of model 1 and model 2 in the (A) training and (B) validation cohorts. AUC, area under the curve; ROC, receiver operating characteristic.

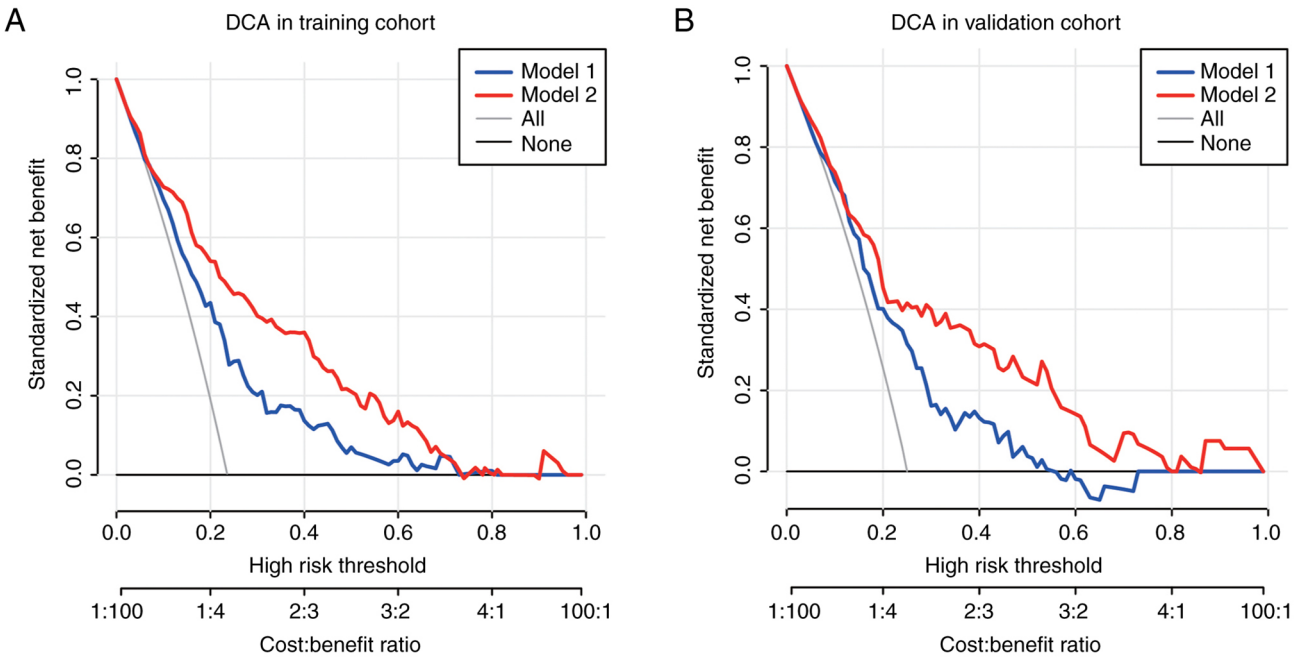

Figure 5. DCA of the nomogram in the (A) training and (B) validation cohorts. DCA, decision curve analysis.

The efforts of researchers focus on the accurate prediction of EC clinicopathological features and subsequent personalized treatment. MI is a well-known predictor of OS and recurrence-free survival in EC, and is essential in making the decision of which adjuvant therapy to apply (12). A previous found that metabolic disorders are closely associated with tumor stage, grade, lymph-vascular space invasion (LVSI) and LNM of EC, therefore representing an independent risk factor of EEC (13). Previous studies analyzed stage I and II cases without adnexal pathological factors, and found that patients with type I EC without depth of MI ≥1/2 had a significant risk of ovarian metastasis and LNM (14,15). However, the association between metabolic abnormalities and MI is not clear. The present study investigated preoperative risk factors of MI and found four features, namely MRS, histological type, LNM and tumor grade, that were independent risk factors for MI in EC. A nomogram was then constructed and validated by combining MRS features and clinical information to assess the depth of MI in patients with EC. Further ROC analysis showed that the predictive value of model 2 for MI was significantly higher than that of model 1, indicating that the addition of MRS significantly improved the predictive accuracy of MI. The calibration plot showed consistency between the training and validation sets. DCA showed that the application of the

combined nomogram including MRS could provide more benefits than the clinicopathological model alone. MRS is also a commonly used indicator and easy to obtain.

The highlight of the present study is the inclusion of the MRS in the predictive model of MI. One study reported direct associations between MetS and EC risk (10). Women with metabolic disorders, including obesity and diabetes, have an increased risk of developing EC. A case-control study from the European Prospective Investigation into Cancer and Nutrition, which analyzed 284 women with EC, found that women with MetS had a relative risk of 2.12 times that of the general population. The same study noticed a positive trend in risk with the increasing number of MetSs. A different study conducted on 135,110 postmenopausal women in the UK identified three independent predictors of EC risk: BMI, body fat percentage and fat mass (16). However, metabolic indicators have so far been neglected in the prediction of EC metastasis. A retrospective study on 506 EC cases revealed that the patients with MetS had a higher positive rate of LNM, LVSI and deep-MI proportion, suggesting that patients with EC and MetS have higher tumor aggressiveness (10). In the present findings, MRS, histological type, LNM and tumor grade were independent factors, and these factors were used to build the model. To the best of our knowledge, there only a few predictive models have been constructed to evaluate MI before surgery, and they are mostly based on MRI radiomics (7,17). The aforementioned studies used parameters such as axial T1-weighted images (T1WIs), T2WIs and diffusion weighted imaging to sketch region of interest, and further least absolute shrinkage and selection operator regression was conducted to narrow the range. The AUC of the clinical parameters, radiomics signature and nomogram in evaluating DMI were 0.744, 0.869 and 0.883, respectively. The predictive accuracy was also very high for the present model in predicting MI, with an AUC value of 0.828 for model 2 in the training group. However, DCA was conducted to further verify the accuracy of the predictive model. While clinical imaging indicators can improve the diagnosis of deep MI in patients with early stage EC, imaging examinations are subjective and depend on the technology used and the skill of the clinician. The previous literature has reported several risk-scoring models for the prediction of MI in patients with EC. One of the key indicators associated with MI is estrogen-related receptor γ (ERRγ) (18). ERRγ overexpression occurs in EC and may be involved in the regulation of glucose metabolism and the promotion of MI in EC. Furthermore, the AUC for ERRγ was reported as 0.834, indicating the good diagnostic performance ERRγ for differentiating between healthy individuals and patients with EC, and that ERRγ may represent a promising non-invasive biomarker for the disease. In the present study, MRS was normally distributed in the patients with EC. MRS was found to be a significant indicator of MI, implying that metabolic mechanisms may be involved in EC invasion. The different components of the score system were not investigated. Another study suggested that HDL-C may be a valuable marker of EC, but there is no direct evidence that it is associated with metastasis (19).

Although the results of the present study indicated that MRS has a significant association with MI, stratified analysis showed that more clear effects were found in certain patients, such as older patients (≥60 years), patients with a higher BMI (≥24 kg/m^2), patients in postmenopausal status, and those without DM or HP. It has been reported that MetSs have a significant influence in specific groups, such as in patients with postoperative complications, or in those with early-stage or low-grade tumors, which is consistent with what was observed in the present study (20-22). Since a good proportion of young patients with EC would like to preserve fertility and, to the best of our knowledge, there have been no such models or studies related to this, we may explore this in the future. The depth of MI is an important indication for fertility preservation treatment in EC, and a future study could explore the relationship between MRS score and MI in patients with EC who wish to preserve fertility. MRS can be added to the predictive model of MI to improve its accuracy.

The present study had a number of limitations. Firstly, all data was derived from a single-center; therefore, further external validation of the nomogram is needed. Secondly, the retrospective nature of this study may lead to potential bias. Finally, although the number of enrolled cases is relatively large, a larger sample size and a randomized control trial are recommended for future studies. Using the nomogram built in the present study, it is possible to adopt more conservative treatment, avoiding extended surgery, which would improve the quality of life of the patients, while high-risk patients can be screened to undertake more aggressive measures.

In conclusion, the present study investigated the effect of MRS in patients with EC and its correlation with MI. With the use of stratified analysis, specific subgroups of patients in which MRS has a stronger influence on MI were found. MRS can significantly improve the accuracy of predicting MI in patients with EC. A nomogram integrating clinical factors and MRS was built that can predict MI in patients with EC. The effectiveness and NB of the model was determined. Given the high incidence of MetSs in EC, monitoring metabolic abnormalities may enable clinicians to identify individuals at high risk at an early stage and provide guidance for a healthy lifestyle.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YQ conceived and designed the experiments, and contributed reagents/materials/analysis tools. LD made contributions to the methodology and statistical analysis, and provided supervision. QZ performed the data collection and analyzed the data. YQ and LD confirm the authenticity of all the raw data.

YQ and LD contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board for Clinical Trials of Nanjing First Hospital (approval number, KY20210604-05). The protocol is described on the hospital website, and subjects were provided the opportunity to opt-out; therefore, no additional consent was required from the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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