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Development and Validation of a Nomogram Prediction Model for Endometrial Malignancy in Patients with Abnormal Uterine Bleeding

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Purpose: This study aimed to identify the risk factors and sonographic variables that could be integrated into a predictive model for endometrial cancer (EC) and atypical endometrial hyperplasia (AEH) in women with abnormal uterine bleeding (AUB).

Materials and Methods: This retrospective study included 1837 patients who presented with AUB and underwent endometrial sampling. Multivariable logistic regression was developed based on clinical and sonographic covariates [endometrial thickness (ET), resistance index (RI) of the endometrial vasculature] assessed for their association with EC/AEH in the development group (n=1369), and a predictive nomogram was proposed. The model was validated in 468 patients.

Results: Histological examination revealed 167 patients (12.2%) with EC or AEH in the development group. Using multivariable logistic regression, the following variables were incorporated in the prediction of endometrial malignancy: metabolic diseases [odds ratio (OR)=7.764, 95% confidence intervals (CI) 5.042–11.955], family history (OR=3.555, 95% CI 1.055–11.971), age ≥40 years (OR=3.195, 95% CI 1.878–5.435), RI ≤0.5 (OR=8.733, 95% CI 4.311–17.692), and ET ≥10 mm (OR=8.479, 95% CI 5.440–13.216). A nomogram was created using these five variables with an area under the curve of 0.837 (95% CI 0.800–0.874). The calibration curve showed good agreement between the observed and predicted occurrences. For the validation group, the model provided acceptable discrimination and calibration.

Conclusion: The proposed nomogram model showed moderate prediction accuracy in the differentiation between benign and malignant endometrial lesions among women with AUB.

Key Words: Endometrial neoplasms, uterine hemorrhage, ultrasonography, risk assessment

INTRODUCTION

Abnormal uterine bleeding (AUB) is a common gynecologic complaint. Early referral of patients presenting with AUB to endometrial sampling plays an important part in the early detection and management of endometrial malignancy. However, endometrial cancer (EC) is present in only 9% of postmenopausal women and 1%–2% of premenopausal women with AUB.[1,2] It stands to reason that the majority of low-risk patients undergo an unnecessary invasive diagnostic procedure, including dilatation and curettage (D&C) or hysteroscopy, for this condition.

Transvaginal ultrasound (TVUS) has been widely employed as a non-invasive first-line test to evaluate AUB. In postmenopausal patients with endometrium ≥4 mm, the risk of EC is considered to be low.[3] However, many women presenting with AUB are premenopausal and perimenopausal, and there is a growing incidence of EC among younger age group. Previous stud-

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ies showed no consent regarding the endometrial thickness (ET) cut-off value to be used for the indication of invasive diagnosis in premenopausal symptomatic women.[4,5] Several predictive models based on clinical variables and sonographic predictors have been developed to estimate the individual risk of EC or atypical endometrial hyperplasia (AEH).[6] Nevertheless, most of them focused on perimenopausal and postmenopausal women, and few have been validated. Moreover, the majority of the existing models are for patients of Caucasian ethnicity. Differences in demographic and clinic characteristics among patients of different races have been observed in EC cases.[7]

In this regard, we sought to develop and validate a nomogram predictive model that includes clinical and ultrasound variables to estimate the probability of EC/AEH in Chinese patients with AUB, including premenopausal, perimenopausal, and postmenopausal women.

MATERIALS AND METHODS

Patient population and data collection

Data from women presenting with AUB between January 2013 and December 2015 at Women's Hospital, Zhejiang University School of Medicine were evaluated retrospectively. Only patients whose preoperative TVUS examination and histopathological findings were fully documented were included in the study. The exclusion criteria included already known malignancies, existing pregnancy, and endometrial sampling within the past 3 months. Complete data sets with information on age, body mass index [BMI=weight (kg)/height^2 (m^2)], menstrual history, medical history (diabetes and hypertension), and family history (endometrium, breast, and colon carcinoma) were available for 1369 patients. Obesity was defined as BMI ≥25 kg/m^2. Patients enrolled in this study underwent either hysteroscopy or D&C after ultrasound examination. Histopathological evaluation of all endometrial samples was performed by gynecologic pathologists. Patients undergoing endometrial evaluation between January 2020 and January 2021 were assigned to the validation group. This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Women's Hospital, Zhejiang University School of Medicine (approval number: IRB-20210233-R). No additional patient informed consent was required, given the retrospective nature of this study.

Doppler measurement technique

ET and endometrial vascularity were examined using color Doppler ultrasonography (GE Voluson 730 Expert or Voluson E8, GE Healthcare, Milwaukee, WI, USA) with a 5–9 MHz transvaginal probe. The spiral arterioles could be visualized within the endometrial layer and measured. The color blood flows would be assessed if dominant vessels were visualized in endometrial lesions. Blood flow velocity waveforms were obtained. The mean resistance index (RI) was measured from 3–5 consecutive cardiac cycles. Maximum thickness of the endometrium was measured in the uterine longitudinal axis and recorded as the sum of both layers.

Statistical analysis

The chi-square test was used to analyze the differences between the development group and validation group. The Kolmogorov-Smirnov test showed that the continuous characteristics data were not normally distributed in this study. Continuous variables were reported as medians with interquartile range (IQR). Categorical variables were reported as whole numbers and proportions. Clinical and demographic variables that showed significant differences in univariate analysis (p<0.05) and variables of clinical importance were the candidate predictor variables for the multivariable logistic regression analysis with backward stepwise selection. Pearson correlation coefficient variance inflation factor was calculated to detect multicollinearity between the chosen variables. The selected variables were incorporated in the nomogram to predict the probability of EC/AEH using the R software (http://www.r-project.org).

Accuracy of the nomogram was evaluated using the receiver-operator characteristic curve (ROC) analysis and the area under the curve (AUC). Calibration was evaluated using a calibration plot to assess the agreement between the nomogram-predicted probabilities and the observed frequencies. All statistical tests were two-sided, and p value <0.05 was considered statistically significant. Statistical analyses were performed with software programs [IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) and R, version 4.1.0].

RESULTS

Clinical characteristics and univariate analysis

A total of 1369 women with a median age of 45 years (IQR, 39–49 years) were included in the development group. Histopathological examination revealed the presence of 167 (12.2%) cases of endometrial carcinoma and AEH. The validation group included 468 individuals. The median age of patients in the validation group was 45 years (IQR, 34–51 years). No significant differences were observed in hypertension, obesity, diabetes, family history, blood flow RI, and ET between the development and validation groups. Table 1 presents a detailed comparison of the predictive variables between the development and validation groups. The validation group was different from the development group in that the former had more patients aged ≥40 years (78.42% vs. 69.17%).

According to the univariate analysis, age, hypertension, obesity, diabetes, family history, blood flow RI, and ET were all significantly associated with EC/AEH (Table 2). Since correlations among type 2 diabetes, obesity, and elevated blood pressure in individuals were widely recognized, the presence of hy-

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Table 1. Patients' Clinical Characteristics

Variables	Development group		Validation group		*p* value*
	EC/AEH (n=167)	Benign (n=1202)	EC/AEH (n=63)	Benign (n=405)	
Age					<0.001
<40 years	25 (15.0)	397 (33.0)	7 (11.1)	94 (23.2)	
≥40 years	142 (85.0)	805 (67.0)	56 (88.9)	311 (76.8)	
Obesity					0.107
No	137 (82.0)	1187 (98.8)	50 (79.4)	395 (97.5)	
Yes	30 (18.0)	15 (1.2)	13 (20.6)	10 (2.5)	
Diabetes					0.096
No	138 (82.6)	1189 (98.9)	54 (85.7)	392 (96.8)	
Yes	29 (17.4)	13 (1.1)	9 (14.3)	13 (3.2)	
Hypertension					0.078
No	121 (72.5)	1161 (96.6)	47 (74.6)	380 (93.8)	
Yes	46 (27.5)	41 (3.4)	16 (25.4)	25 (6.2)	
Metabolic diseases					0.348
No	91 (54.5)	1119 (93.1)	37 (58.7)	369 (91.1)	
Yes	76 (45.5)	83 (6.9)	26 (41.3)	36 (8.9)	
Family history					0.676
No	157 (94.0)	1195 (99.4)	58 (92.1)	405 (100)	
Yes	10 (6.0)	7 (0.6)	5 (7.9)	0	
ET					0.073
<10 mm	95 (56.9)	1126 (93.7)	40 (63.5)	363 (89.6)	
≥10 mm	72 (43.1)	76 (6.3)	23 (36.5)	42 (10.4)	
RI					0.391
>0.5	137 (82.0)	1180 (98.2)	45 (71.4)	401 (99.0)	
≤0.5	30 (18.0)	22 (1.8)	18 (28.6)	4 (1.0)	

EC, endometrial cancer; AEH, atypical endometrial hyperplasia; ET, endometrial thickness; RI, resistance index.
Data are presented as n (%).
*Comparison of the frequency of predictive variables in the development and validation groups.

pertension, obesity, and diabetes in this study was interpreted as metabolic disease, which was found to be strongly associated with EC/AEH as well (Table 2).

Development of the prediction model and nomogram

Established risk factors, as well as variables of clinical importance, were selected for the prediction model. There were no significant interactions between the variables. Backward stepwise selection in the multivariable logistic regression modeling identified metabolic diseases, family history, age ≥40 years, RI ≤0.5, and ET ≥10 mm as potential independent risk factors for EC/AEH. Table 2 presents the associated odds ratios of the predictive variables in the development group. Nomogram to predict the risk of EC/AEH is shown in Fig. 1. The nomogram to predict the risk of EC/AEH was constructed and incorporated variables from the final multivariable model, including the presence of metabolic diseases, family history, age, RI, and ET. A total score was calculated by summing up the assigned number of points for each factor in the nomogram, and we were able to get the estimated predicted probability for the presence of EC/AEH.

Model performance and validation

To further assess the discriminative ability of the model, the ROC curve analysis was used. The AUC was 0.837 [95% confidence interval (CI) 0.800–0.874] for the development group and 0.912 (95% CI 0.881–0.943) for the validation group (Fig. 2). The potential model overfitting was assessed by bootstrap validation with 1000 resamplings. The calibration plot for the prediction of risk of EC/AEH is shown in Fig. 3. Tests showed that the predicted and observed values were close in the development group (p=0.889) and in the validation group (p=0.3528).

DISCUSSION

Existing guidelines recommend considering risk factors such as age, metabolic syndrome (obesity, hypertension, diabetes), and increased ET when evaluating AUB. However, the best combination of these factors used for the decision to perform endometrial sampling to rule out EC/AEH is not yet defined, and the optimal strategy for risk stratification of women with AUB is unclear, especially in pre- and peri-menopausal women. In this study, we developed a nomogram for the prediction of

Table 2. Analysis of the Development Group by Univariate and Multivariable Logistic Regressions

Variables	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age				
<40 years	Reference		Reference	
≥40 years	2.801 (1.801–4.357)	<0.001	3.195 (1.878–5.435)	<0.001
Obesity				
No	Reference			
Yes	17.328 (9.096–33.012)	<0.001		
Diabetes				
No	Reference			
Yes	19.220 (9.761–37.844)	<0.001		
Hypertension				
No	Reference			
Yes	10.765 (6.791–17.065)	<0.001		
Metabolic diseases				
No	Reference		Reference	
Yes	11.260 (7.720–16.423)	<0.001	7.764 (5.042–11.955)	<0.001
Family history				
No	Reference		Reference	
Yes	10.874 (4.081–28.975)	<0.001	3.555 (1.055–11.971)	0.042
ET				
<10 mm	Reference		Reference	
≥10 mm	11.229 (7.645–16.492)	<0.001	8.479 (5.440–13.216)	<0.001
RI				
>0.5	Reference		Reference	
≤0.5	11.745 (6.590–20.933)	<0.001	8.733 (4.311–17.692)	<0.001

OR, odds ratio; CI, confidence interval; ET, endometrial thickness; RI, resistance index.

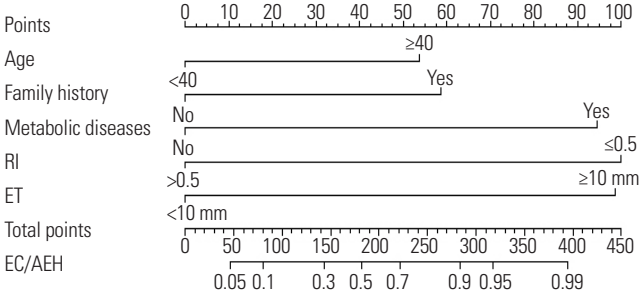

Fig. 1. Nomogram predicting the probability of EC/AEH of patients with AUB. For each patient, lines are drawn upward to determine the points received from the five variables. The sum of the points obtained for each covariate is located on the "Total Points" axis. A line is drawn downward to the bottom scale to determine the possibility of EC/AEH. EC, endometrial cancer; AEH, atypical endometrial hyperplasia; ET, endometrial thickness; RI, resistance index.

endometrial malignancy based on sonographic and clinical characteristics, which can be used to make individualized decisions regarding the further invasive diagnostic procedures and treatment. To our knowledge, this is the first nomogram predictive model for endometrial malignancy in women with AUB. The nomogram was developed using a large population from a tertiary hospital, and the discriminatory ability and accurate calibration was rigorously assessed and externally validated.

TVUS was recommended as a first-line test in patients with AUB, as it is readily accessible and cost-effective. ET among postmenopausal women with AUB below 4 mm seems to be associated with a very low risk of EC.[8] Unfortunately, there is no established consensus on the threshold for ET for premenopausal women. In accordance with the results of other studies, our data indicated that patients with thicker endometrium exhibited a higher risk of endometrial malignancy. Previous studies showed that an ET >10–11 mm was one of the predictors associated with endometrial malignancy among symptomatic women.[5,9,10] Bivariate cut-off for an ET at 10 mm was chosen in our study, as this value was close to the optimal mathematical value according to logistic regression.

A high proportion of women presenting with AUB has anatomical abnormalities, such as fibroids and adenomyosis. In such circumstances, satisfactory visualization of the endometrium cannot be made and ET measurement is unreliable. Moreover, thick endometrium could probably result from benign pathologies, such as polyps. Our study showed that Doppler ultrasound examination can contribute to a correct prediction of endometrial malignancy. We measured the RI of the vessels in endometrial lesions. A significantly low value for

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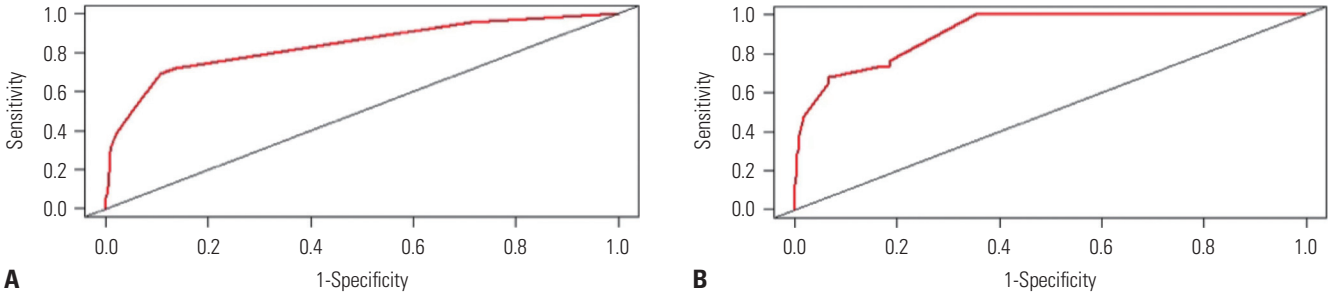

Fig. 2. ROC curves of the nomogram to predict the probability of EC/AEH for the development group (A) and validation group (B). ROC, receiveroperator characteristic curve; EC, endometrial cancer; AEH, atypical endometrial hyperplasia.

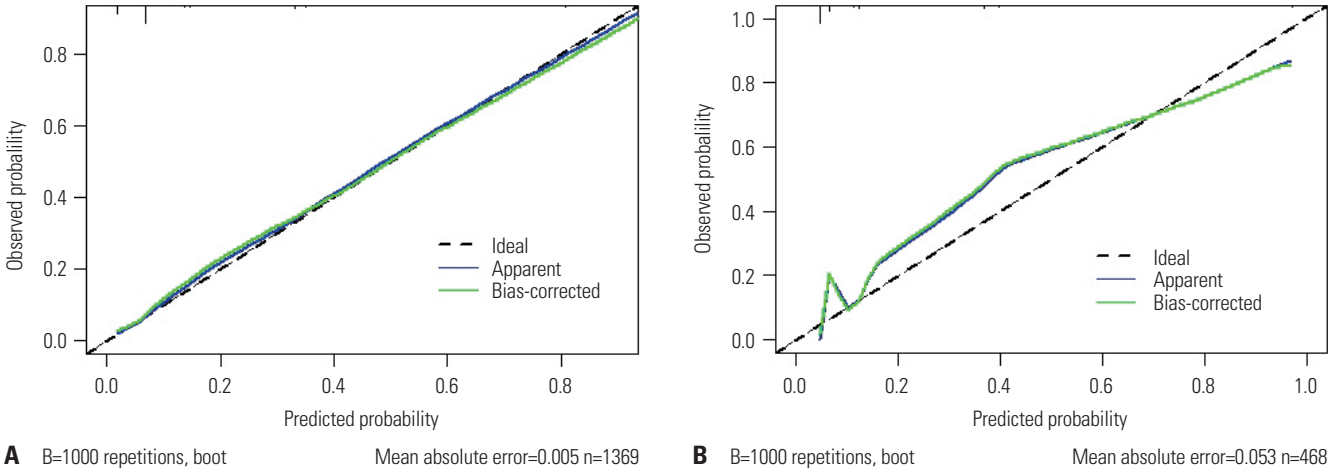

Fig. 3. Calibration curves show the association between the probability of EC/AEH as predicted by the model and the observed EC/AEH rate for the development group (A) and validation group (B). Y-axis expresses the actual EC/AEH rate. X-axis represents the predicted EC/AEH probability. Diagonal black dotted lines indicate an ideal model. Blue line represents the performance of the nomogram. A closer distance between two curves indicates higher accuracy. EC, endometrial cancer; AEH, atypical endometrial hyperplasia.

RI was found compared to that of nonmalignant endometrium, and we used a cutoff value of 0.5. In agreement with our results, Nasheeha and Gk[11] found that spiral artery RI ≤0.5 helps in differentiating malignant from benign endometrial pathology. Ultrasound-based model and scoring systems including several ultrasound features, such as ET and echogenicity, the presence of blood vessels, their number and type of branching, were developed for the risk assessment.[12] These models can significantly improve the diagnostic performance compared to prior models that simply include clinical parameters and ET. However, collecting parameters of the scan and calculating the scores is too cumbersome for clinical use. Another drawback is interobserver variation in the assessment of different parameters, especially in non-expert operators. It is a strength that the ultrasound variables in our nomogram model are easily obtained, even if one is only a moderately experienced examiner.

Recent studies have found that metabolic syndromes (diabetes, hypertension, and obesity) were strongly associated with the occurrence of EC and endometrial atypical hyperplasia.[13] Studies have suggested chronic inflammation and hyperestrogenia in obesity induce the occurrence and development of EC. In addition, molecules related to metabolic syndrome can accelerate the transformation of normal endometrial cells to malignancy by further remodeling the immune microenvironment.[14] Taking into account the close clinical correlation among diabetes, hypertension, and obesity, we used metabolic diseases as the shrinkage of these three variables. Obesity was defined as BMI ≥30 kg/m^2 according to the World Health Organization standards. A recent study from India reported that BMI ≥25 kg/m^2 increases the risk for EC/AEH in premenopausal women with AUB.[15] In our study, obesity was defined as BMI ≥25 kg/m^2, which is suitable for Asian population characteristics.

Corbacioglu Esmer et al.[16] found that the prevalence of endometrial hyperplasia and malignancy was significantly higher in women aged 40–45 years and >45 years compared to younger women. A previous review concluded that there was a significantly increased risk of AEH/EC for symptomatic women aged 40–50 years compared to those aged <40 years.[1] Patients aged ≥45 years were mostly perimenopausal and postmenopausal women, for whom endometrial sampling are usually recommended if they present AUB.[17] These facts indicate the importance of endometrial sampling, especially for the diagnosis of premalignant lesions (such as hyperplasia) in women aged over 40 years presenting with AUB. The existing evidence indicates that 40 years is an appropriate cutoff age for model developing.

Reproductive factors played an important part in the inci-

dence of EC. Significant reduction in EC incidence was found among parous women compared to nulliparous women.[18] The protective effect of pregnancy against carcinogenesis in endometrium can be explained by the mechanism of EC that prolonged exposure to estrogen increases uncontrolled differentiation of endometrium cells, whereas progesterone opposes this effect.[19] However, the higher risk among nulliparous women could potentially stem from anovulatory infertility, which was less analyzed in the published literature. Besides, late menarche, use of combined oral contraceptives, and increased age at last delivery reduced the risk of EC. In view of a variety of reproductive factors and hormone-related exposures involved among the population in this study, we did not include the data on certain factors, such as exogenous hormone use, age of menarche, and parity, to keep the model simple. Therefore, their effects in the model could not be assessed.

The main weakness of the present study is related to its single-center retrospective design. Second, since missing observations were excluded from the analysis, bias was inevitable. In this study, TVUS was performed on the day when patients visited the office; therefore, the timing of ET measurement in relation to the menstrual cycle in premenopausal women was not standardized. Finally, the nomogram in this study may require further validation from cohorts at other medical centers to evaluate its clinical value.

In conclusion, the proposed nomogram had a moderate diagnostic accuracy in predicting endometrial malignant lesions among women with AUB. It may serve as a simple and straightforward tool that is of particular interest for clinicians in making a decision on further workup.

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AUTHOR CONTRIBUTIONS

Conceptualization: Hengchao Ruan and Suhan Chen. Data curation: Linjuan Ma and Jingyi Li. Formal analysis: Suhan Chen and Qian Ying. Funding acquisition: Jianhong Zhou. Investigation: Yizhou Huang and Jie Luo. Methodology: Suhan Chen and Qian Ying. Project administration: Hengchao Ruan and Suhan Chen. Resources: Hengchao Ruan and Jianhong Zhou. Software: Suhan Chen. Supervision: Jianhong Zhou. Validation: Qian Ying. Visualization: Suhan Chen. Writing—original draft: Suhan Chen and Jingyi Li. Writing—review & editing: Hengchao Ruan and Jianhong Zhou. Approval of final manuscript: all authors.

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REFERENCES

1. Pennant ME, Mehta R, Moody P, Hackett G, Prentice A, Sharp SJ, et al. Premenopausal abnormal uterine bleeding and risk of endometrial cancer. BJOG 2017;124:404-11.
2. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. JAMA Intern Med 2018;178:1210-22.
3. Committee on Gynecologic Practice. The role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. Obstet Gynecol 2018;131:e124-9.
4. Kim MJ, Kim JJ, Kim SM. Endometrial evaluation with transvaginal ultrasonography for the screening of endometrial hyperplasia or cancer in premenopausal and perimenopausal women. Obstet Gynecol Sci 2016;59:192-200.
5. Kumari P, Gaikwad HS, Nath B. Endometrial cut off thickness as predictor of endometrial pathology in perimenopausal women with abnormal uterine bleeding: a cross-sectional study. Obstet Gynecol Int 2022;2022:5073944.
6. Alblas M, Velt KB, Pashayan N, Widschwendter M, Steyerberg EW, Vergouwe Y. Prediction models for endometrial cancer for the general population or symptomatic women: a systematic review. Crit Rev Oncol Hematol 2018;126:92-9.
7. Sarink D, Wilkens LR, White KK, Le Marchand L, Wu AH, Setiawan VW, et al. Racial/ethnic differences in anthropometric and hormone-related factors and endometrial cancer risk: the Multiethnic Cohort Study. Br J Cancer 2021;124:1724-33.
8. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol 2010;116:160-7.
9. Giannella L, Cerami LB, Setti T, Bergamini E, Boselli F. Prediction of endometrial hyperplasia and cancer among premenopausal women with abnormal uterine bleeding. Biomed Res Int 2019;2019:8598152.
10. Heremans R, Van Den Bosch T, Valentin L, Wynants L, Pascual MA, Fruscio R, et al. Ultrasound features of endometrial pathology in women without abnormal uterine bleeding: results from the international endometrial tumor analysis study (IETA3). Ultrasound Obstet Gynecol 2022;60:243-55.
11. Nasheeha N, Gk P. Diagnostic accuracy of uterine artery and spiral artery Doppler for evaluation of endometrial pathology in postmenopausal bleeding. J Gynecol Obstet Hum Reprod 2021;50:102209.
12. Dueholm M, Møller C, Rydbjerg S, Hansen ES, Ørtoft G. An ultrasound algorithm for identification of endometrial cancer. Ultrasound Obstet Gynecol 2014;43:557-68.
13. Zhang H, Kong W, Han C, Liu T, Li J, Song D. Correlation of metabolic factors with endometrial atypical hyperplasia and endometrial cancer: development and assessment of a new predictive nomogram. Cancer Manag Res 2021;13:7937-49.
14. Yang X, Wang J. The role of metabolic syndrome in endometrial cancer: a review. Front Oncol 2019;9:744.
15. Jha S, Singh A, Sinha HH, Bhadani P, Anant M, Agarwal M. Rate of premalignant and malignant endometrial lesion in "low-risk" pre-

menopausal women with abnormal uterine bleeding undergoing endometrial biopsy. Obstet Gynecol Sci 2021;64:517-23.
16. Corbacioglu Esmer A, Akbayir O, Goksedef BP, Gunduz N, Kisacık S, Dagdeviren H, et al. Is there an appropriate cutoff age for sampling the endometrium in premenopausal bleeding? Gynecol Obstet Invest 2014;77:40-4.
17. Papakonstantinou E, Adonakis G. Management of pre-, peri-, and post-menopausal abnormal uterine bleeding: when to perform endometrial sampling? Int J Gynaecol Obstet 2022;158:252-9.
18. Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, et al. Risk factors for endometrial cancer: an umbrella review of the literature. Int J Cancer 2019;145:1719-30.
19. Ali AT. Reproductive factors and the risk of endometrial cancer. Int J Gynecol Cancer 2014;24:384-93.