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Estimating risk of endometrial malignancy and other intracavitary uterine pathology in women without abnormal uterine bleeding using IETA-1 multinomial regression model: validation study

R. HEREMANS[1,2], L. WYNANTS[2,3], L. VALENTIN[4], F. P. G. LEONE[5], M. A. PASCUAL[6], R. FRUSCIO[7], A. C. TESTA[8], F. BUONOMO[9], S. GUERRIERO[10], E. EPSTEIN[11], T. BOURNE[2,12], D. TIMMERMAN[1,2] and T. VAN DEN BOSCH[1,2], for the IETA Consortium

[1]*Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium;* [2]*Department of Development and Regeneration, KU Leuven, Leuven, Belgium;* [3]*Department of Epidemiology, CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands;* [4]*Department of Obstetrics and Gynecology, Skåne University Hospital Malmö and Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden;* [5]*Department of Obstetrics and Gynecology, Clinical Sciences Institute Luigi Sacco, Milan, Italy;* [6]*Department of Obstetrics, Gynecology and Reproduction, Hospital Universitario Dexeus, Barcelona, Spain;* [7]*UOC Gynecology, Department of Medicine and Surgery, University of Milan-Bicocca, Fondazione IRCCS San Gerardo dei Tontori, Monza, Italy;* [8]*Dipartimento Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitatio A Gemelli, IRCCS, Rome, Italy;* [9]*Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy;* [10]*Department of Obstetrics and Gynecology, University of Cagliari, Policlinico Universitario Duilio Casula, Monserrato, Cagliari, Italy;* [11]*Department of Clinical Science and Education, Karolinska Institutet, and Department of Obstetrics and Gynecology, Södersjukhuset, Stockholm, Sweden;* [12]*Department of Obstetrics and Gynaecology, Queen Charlotte's and Chelsea Hospital, Imperial College London, London, UK*

KEYWORDS: asymptomatic disease; decision support techniques; diagnosis; endometrial neoplasms; endometrium; incidental findings; ultrasonography

CONTRIBUTION

What are the novel findings of this work?
This is the first study to test the International Endometrial Tumor Analysis (IETA)-1 prediction model for intracavitary uterine pathology in women without abnormal uterine bleeding. Our study shows that the model discriminates between benign and malignant intracavitary conditions in asymptomatic women more accurately than does endometrial thickness alone, but it overestimates the risk of endometrial cancer.

What are the clinical implications of this work?
The IETA-1 risk prediction model can facilitate patient counseling about endometrial status in asymptomatic women, taking into consideration the potential for overestimation of the risk of malignancy.

ABSTRACT

Objectives *To assess the ability of the International Endometrial Tumor Analysis (IETA)-1 polynomial regression model to estimate the risk of endometrial cancer (EC) and other intracavitary uterine pathology in women without abnormal uterine bleeding.*

Methods *This was a retrospective study, in which we validated the IETA-1 model on the IETA-3 study cohort (n = 1745). The IETA-3 study is a prospective observational multicenter study. It includes women without vaginal bleeding who underwent a standardized transvaginal ultrasound examination in one of seven ultrasound centers between January 2011 and December 2018. The ultrasonography was performed either as part of a routine gynecological examination, during follow-up of non-endometrial pathology, in the work-up before fertility treatment or before treatment for uterine prolapse or ovarian pathology. Ultrasonographic findings were described using IETA terminology and were compared with histology, or with results of clinical and ultrasound follow-up of at least 1 year if endometrial sampling was not performed. The IETA-1 model, which was created using data from patients with abnormal uterine bleeding, predicts four histological outcomes: (1) EC or endometrial intraepithelial neoplasia (EIN); (2) endometrial polyp or intracavitary myoma; (3) proliferative or secretory endometrium, endometritis, or endometrial hyperplasia without atypia;*

Correspondence to: Prof. T. Van den Bosch, Department of Obstetrics and Gynecology, University Hospitals KU Leuven, Herestraat 49, 3000 Leuven, Belgium (e-mail: thierry.vandenbosch@uzleuven.be)

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and (4) endometrial atrophy. The predictors in the model are age, body mass index and seven ultrasound variables (visibility of the endometrium, endometrial thickness, color score, cysts in the endometrium, non-uniform echogenicity of the endometrium, presence of a bright edge, presence of a single dominant vessel). We analyzed the discriminative ability of the model (area under the receiver-operating-characteristics curve (AUC); polytomous discrimination index (PDI)) and evaluated calibration of its risk estimates (observed/expected ratio).

Results *The median age of the women in the IETA-3 cohort was 51 (range, 20–85) years and 51% (887/1745) of the women were postmenopausal. Histology showed EC or EIN in 29 (2%) women, endometrial polyps or intracavitary myomas in 1094 (63%), proliferative or secretory endometrium, endometritis, or hyperplasia without atypia in 144 (8%) and endometrial atrophy in 265 (15%) women. The endometrial sample had insufficient material in five (0.3%) cases. In 208 (12%) women who did not undergo endometrial sampling but were followed up for at least 1 year without clinical or ultrasound signs of endometrial malignancy, the outcome was classified as benign. The IETA-1 model had an AUC of 0.81 (95% CI, 0.73–0.89, n = 1745) for discrimination between malignant (EC or EIN) and benign endometrium, and the observed/expected ratio for EC or EIN was 0.51 (95% CI, 0.32–0.82). The model was able to categorize the four histological outcomes with considerable accuracy: the PDI of the model was 0.68 (95% CI, 0.62–0.73) (n = 1532). The IETA-1 model discriminated very well between endometrial atrophy and all other intracavitary uterine conditions, with an AUC of 0.96 (95% CI, 0.95–0.98). Including only patients in whom the endometrium was measurable (n = 1689), the model's AUC was 0.83 (95% CI, 0.75–0.91), compared with 0.62 (95% CI, 0.52–0.73) when using endometrial thickness alone to predict malignancy (difference in AUC, 0.21; 95% CI, 0.08–0.32). In postmenopausal women with measurable endometrial thickness (n = 848), the IETA-1 model gave an AUC of 0.81 (95% CI, 0.71–0.91), while endometrial thickness alone gave an AUC of 0.70 (95% CI, 0.60–0.81) (difference in AUC, 0.11; 95% CI, 0.01–0.20).*

Conclusion *The IETA-1 model discriminates well between benign and malignant conditions in the uterine cavity in patients without abnormal bleeding, but it overestimates the risk of malignancy. It also discriminates well between the four histological outcome categories. © 2023 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

With ultrasonography being on the rise as an accessible, first-line pelvic assessment tool, increasingly, uterine abnormalities are picked up in women without abnormal vaginal bleeding or other gynecological symptoms[1–3]. There is no consensus on the appropriate work-up for abnormal ultrasound appearance of the endometrium detected incidentally in women without abnormal uterine bleeding, herein referred to as 'asymptomatic' women. In women with abnormal uterine bleeding, a thickened endometrium indicates endometrial pathology[4]. Seeking additional information on the grayscale ultrasound morphology and vascularization of the endometrium using color or power Doppler ultrasound has been advocated by an international group of experts in the field of gynecological ultrasound[5], because it improves discrimination between benign and malignant endometrium and is helpful for distinguishing different histopathological diagnoses in the uterine cavity[3,4,6]. The International Endometrial Tumor Analysis (IETA) study number 1 (IETA-1), which included women with abnormal vaginal bleeding, described the typical sonographic features of different histological endpoints using the standardized IETA terminology. Moreover, it showed which ultrasound features can rule out endometrial cancer (EC) safely[4]. The IETA group also constructed a multinomial regression model (IETA-1 model) including clinical factors and ultrasound variables to estimate the likelihood of four outcome categories in women with abnormal uterine bleeding: (1) EC or endometrial intraepithelial neoplasia (EIN); (2) endometrial polyp or intracavitary myoma; (3) proliferative or secretory endometrium, endometritis, or endometrial hyperplasia without atypia; and (4) endometrial atrophy[7]. Such a model could be helpful in clinical practice to help tailor further management and guide the decision between no endometrial sampling, follow-up ultrasound, blind endometrial sampling or hysteroscopic resection of intracavitary lesions.

The aim of this study was to assess the performance of the IETA-1 model when applied in asymptomatic pre- and postmenopausal patients. The primary aim was to assess the model's ability to distinguish malignant from benign intracavitary conditions and the calibration of its malignancy predictions. The secondary aim was to assess how adequately the model distinguishes between the four outcome categories and the calibration of these predictions.

METHODS

This was a retrospective study, in which we validated the IETA-1 model on the IETA-3 study cohort ($n = 1745$). The IETA-3 study was a prospective observational multicenter study conducted by the IETA consortium. The intention was to recruit consecutively premenopausal women aged 18 years or more and postmenopausal women, without abnormal uterine bleeding. Seven secondary or tertiary centers specialized in gynecological ultrasonography in three countries (Belgium, Italy and Spain) recruited patients to the study between 1 January 2011 and 31 December 2018. The study was approved by the Leuven ethics committee EC Research (S52897 / ML7087) and by the ethics committees of all participating centers.

All patients gave oral informed consent to participate. Women were recruited either at routine gynecological

examination, during follow-up of non-endometrial pathology, in the work-up before fertility treatment or before treatment for uterine prolapse or ovarian pathology. The women underwent a standardized transvaginal ultrasound examination, with findings described using IETA terminology[5], and the results were recorded in a dedicated web-based datasheet (Clinical Data Miner (CDM), ESAT-STADIUS, KU Leuven, Belgium), which generated warnings in case of incomplete input[8]. Patients underwent endometrial sampling or were followed up for at least 1 year. In the latter group, if there were no clinical or ultrasound signs of endometrial malignancy at 1 year of follow-up or later (range, 12–60 months), the outcome was classified as benign. Histology was evaluated using endometrial samples obtained via an outpatient endometrial sampling device, dilatation and curettage, hysteroscopic resection, or hysterectomy within 120 days following the inclusion scan. Tumor histology was determined locally without central pathology review. The study protocol did not include restrictions for clinician–pathologist interaction. The clinical and sonographic information provided to the pathologist was at the discretion of the recruiting physician.

The IETA-1 model included two clinical predictors: age (in years) and body mass index (BMI) (in kg/m^2); and seven ultrasound predictors: visibility of the endometrium (yes or no); endometrial thickness (in mm); presence of a bright edge (yes or no); IETA color score; presence of a single dominant vessel (yes or no); non-uniform endometrial echogenicity (yes or no); and presence of endometrial cysts (yes or no). If the endometrium was not visible, the value of all other sonographic predictors was set to zero (binary variables received a value of zero; other variables (e.g. color score) received a value so that the scaled value became zero)[7]. The predictors were selected based on expert opinion. Model coefficients and required transformations for all nine parameters are provided in Table S1, and the predicted risk for each outcome category was obtained based on the coefficients presented in Table S1. To obtain the linear predictor (lp), predictor values were multiplied by their coefficients and added to the intercept. To obtain the estimated risk from the lp, the following equation was applied: $\exp(lp_{\text{category of interest}})/[\exp(lp_{\text{endometrial cancer or endometrial intraepithelial neoplasia}}) + \exp(lp_{\text{endometrial polyp or intracavitary myoma}}) + \exp(lp_{\text{proliferative/secretory changes,endometritis,or hyperplasia without atypia}}) + \exp(lp_{\text{endometrial atrophy}})]$. Appendix S1 shows how to perform a risk calculation, using information from patients in the IETA-3 database.

Statistical analysis

Only patients without missing information on model predictors or outcome were included (complete-cases analysis). No formal sample-size calculation was performed. However, like in the IETA-1 study, and in order to test the IETA-1 model, we aimed to recruit about 2000 women.

For assessment of the primary aim (malignancy *vs* no malignancy), we used the data of patients with histological confirmation and of those without histological confirmation who had been followed up for ≥ 1 year. The model outcome was divided into two categories: confirmed EC and/or EIN; and no evidence of EC or EIN. To test the model's ability to predict correctly endometrial malignancy, we included all women ($n = 1745$). To compare the model's ability to discriminate between benign and malignant endometrium with that of endometrial thickness alone, we included only women with visible and measurable endometrium ($n = 1689$). To assess the model's ability to predict correctly the four histological outcomes, we included only women with a histologically confirmed diagnosis ($n = 1532$).

To evaluate the model's ability to discriminate between benign and malignant endometrium, we calculated the sensitivity, specificity, positive (LR+) and negative (LR−) likelihood ratios, accuracy and area under the receiver-operating-characteristics curve (AUC). In a subgroup analysis, we computed the AUC of the model and of endometrial thickness alone for postmenopausal women.

To describe the model's ability to discriminate between the four outcome categories, we calculated pairwise AUCs (conditional risk method) and the polytomous discrimination index (PDI). As four outcome categories were assessed, random discrimination would result in a PDI of 0.25, while perfect discrimination would give a PDI of 1. The accuracy of predicted probabilities is presented as observed/expected ratios, which ideally should be 1[9]. In a *post-hoc* analysis, we also calculated the AUC to distinguish between atrophy and all other categories. For AUC, PDI and observed /expected ratio we present 95% CIs.

Statistical analysis was performed using R statistical package version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). We adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines[10] (Appendix S2).

RESULTS

The median age of the 1745 women in the IETA-3 cohort was 51 (range, 20–85) years and 51% (887/1745) of the women were postmenopausal. Definitive histological confirmation was obtained from endometrial sampling using an outpatient endometrial sampling device in 100 women, dilatation and curettage in 23, hysteroscopic resection in 1052 and hysterectomy in 362. In 11.9% (208/1745) of women, histology was not obtained and in five (0.3%) the sample had insufficient material; these were considered benign for analyses investigating benign *vs* malignant but could not be included in analyses of histological outcome. Histology showed EC or EIN in 1.7% (29/1745) of the women, and 86.2% (25/29) of these were postmenopausal. A detailed description of patient selection, demographic background data and ultrasound findings in the IETA-3 study cohort can be found elsewhere[3]. No endometrial malignancy was diagnosed in the group of 208 that were followed up clinically and sonographically for at least 1 year (range, 12–60 months).

Figure 1 shows which patients were included in the different statistical analyses.

Tables S2 and S3 show the distribution of the model predictors in the IETA-3 validation cohort and the IETA-1 model development cohort. Women in the validation cohort tended to be older and to have a lower BMI than those in the development cohort. Endometrial thickness was lower in the validation cohort than in the development cohort, and the endometria in the validation cohort were less vascularized and more frequently had a single dominant vessel, non-uniform echogenicity and endometrial cysts than had those in the development cohort. EC or EIN constituted 1.7% (29/1745) of the validation data, compared with 6.4% (155/2417) of the development data. Endometrial polyps or intracavitary myomas accounted for 62.7% (1094/1745) of the IETA-3 validation cohort, compared with 40.2% (972/2417) of the IETA-1 development cohort. Proliferative or secretory endometrial changes, endometritis, or endometrial hyperplasia without atypia represented 8.3% (144/1745) of the IETA-3 validation cohort, compared with 32.3% (780/2417) of the IETA-1 development cohort. Endometrial atrophy was recorded in 15.2% (265/1745) of the IETA-3 validation data, compared with 9.3% (224/2417) of the IETA-1 development data.

The IETA-1 model's AUC for discrimination between benign and malignant outcomes ($n = 1745$, including patients with or without histological confirmation) was 0.81 (95% CI, 0.73–0.89). Including only patients in whom the endometrium was visible and measurable ($n = 1689$), the model's AUC was 0.83 (95% CI, 0.75–0.91) compared with 0.62 (95% CI, 0.52–0.73) when using endometrial thickness alone to predict malignancy (difference in AUC, 0.21; 95% CI, 0.08–0.32) (Figure 2). The model overestimated the risk of malignancy, the observed/expected ratio for EC or EIN in our entire cohort ($n = 1745$) being 0.51 (95% CI, 0.32–0.82). The observed/expected ratio for polyps or myomas was 1.08 (95% CI, 1.05–1.11), for proliferative or secretory endometrium, endometritis, or hyperplasia without atypia was 0.42 (95% CI, 0.34–0.51) and for atrophy was 0.81 (95% CI, 0.74–0.89). The model discriminated better

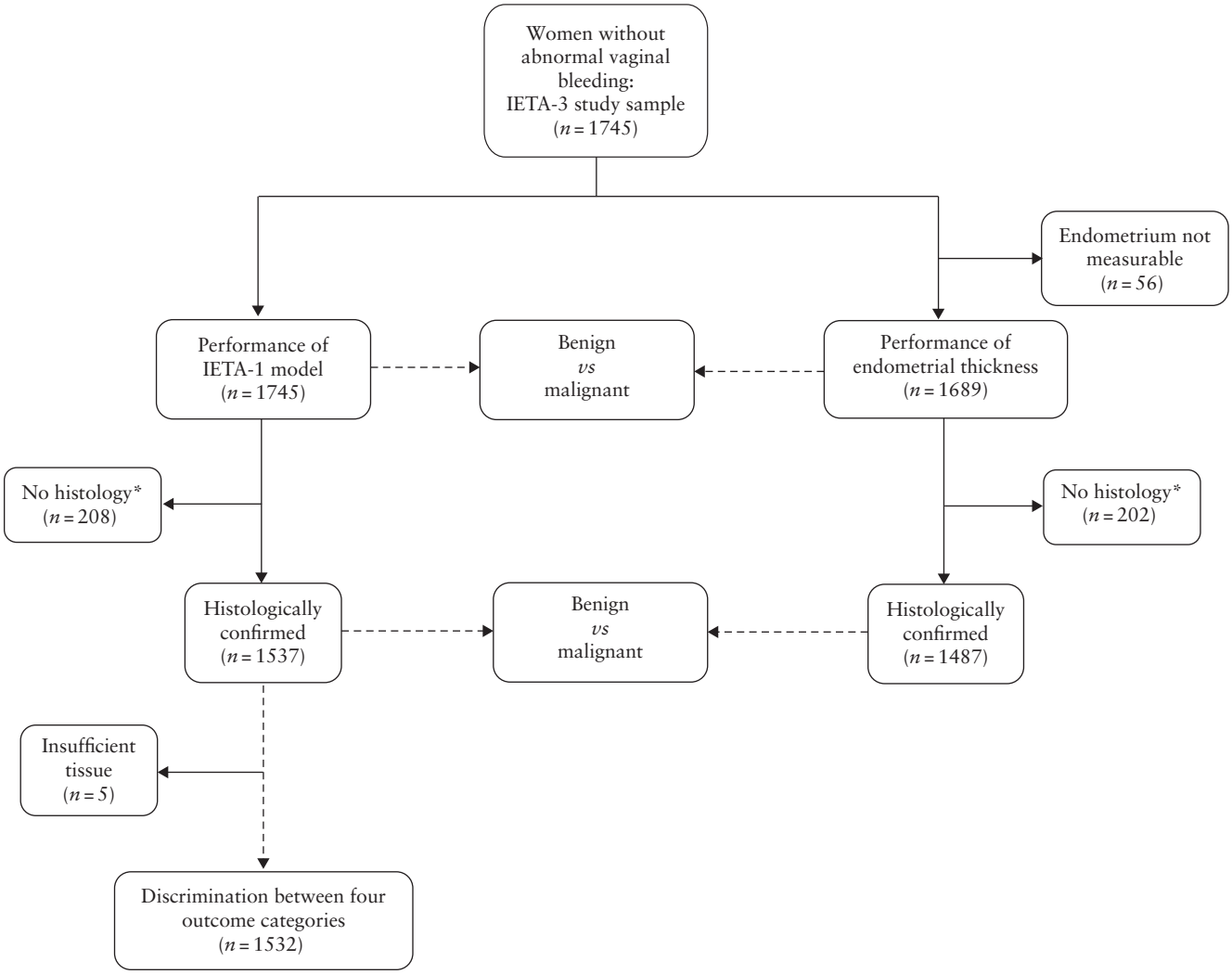

Figure 1 Flowchart summarizing patient selection. *No histological confirmation but with no clinical or sonographic signs of malignancy over ≥ 1 year of follow-up (range, 12–60 months). No malignancy was diagnosed during follow-up. IETA, International Endometrial Tumor Analysis.

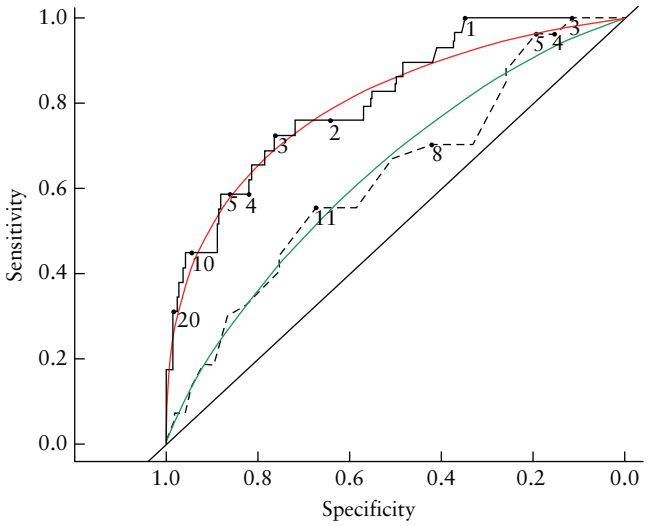

Figure 2 Receiver-operating-characteristics (ROC) curves showing ability to discriminate between benign endometrium and malignant endometrium (endometrial cancer or endometrial intraepithelial neoplasia) of the International Endometrial Tumor Analysis (IETA)-1 model (——) (area under the ROC curve (AUC), 0.83; 95% CI, 0.75–0.91) and sonographic endometrial thickness alone (- - - -) (AUC, 0.62; 95% CI, 0.52–0.73). Smoothed ROC curves for the mathematical model (——) and endometrial thickness alone (——) were obtained via scatterplot smoothing. Numbers represent thresholds (at or above) for each method (in % risk of malignancy for mathematical model; in mm for endometrial thickness). Results are based on women with visible and measurable endometrium ($n = 1689$).

between malignancy (EC or EIN) and endometrial atrophy (AUC, 0.96; 95% CI, 0.94–0.98) than it did between malignancy and proliferative or secretory endometrium, endometritis, or hyperplasia without atypia (AUC, 0.88; 95% CI, 0.83–0.94) and than it did between malignancy and endometrial polyps or intracavitary myomas (AUC, 0.80; 95% CI, 0.72–0.89) (Figure 3). The model was able to categorize the four histological outcomes with considerable accuracy: the PDI was 0.68 (95% CI, 0.62–0.73). Endometrial atrophy was the benign outcome that was most easily distinguishable by the model from the other benign histological outcomes, with an AUC of 0.97 (95% CI, 0.96–0.98) when compared with intracavitary polyps or myomas, and an AUC of 0.93 (95% CI, 0.90–0.96) when compared with proliferative or secretory endometrium, endometritis, or hyperplasia without atypia. The AUC of the IETA-1 model to discriminate between endometrial atrophy and all other intracavitary uterine conditions was 0.96 (95% CI, 0.95–0.98). The model had difficulties distinguishing endometrial polyps or intracavitary myomas from proliferative or secretory endometrium, endometritis, or hyperplasia without atypia (AUC, 0.78; 95% CI, 0.74–0.82).

In postmenopausal women ($n = 887$, including patients with or without histological confirmation), the IETA-1 model had an AUC of 0.77 (95% CI, 0.67–0.88) for discrimination between benign and malignant outcomes. In postmenopausal women with measurable endometrial thickness ($n = 848$, including patients with or without histological confirmation), the IETA-1 model gave an AUC

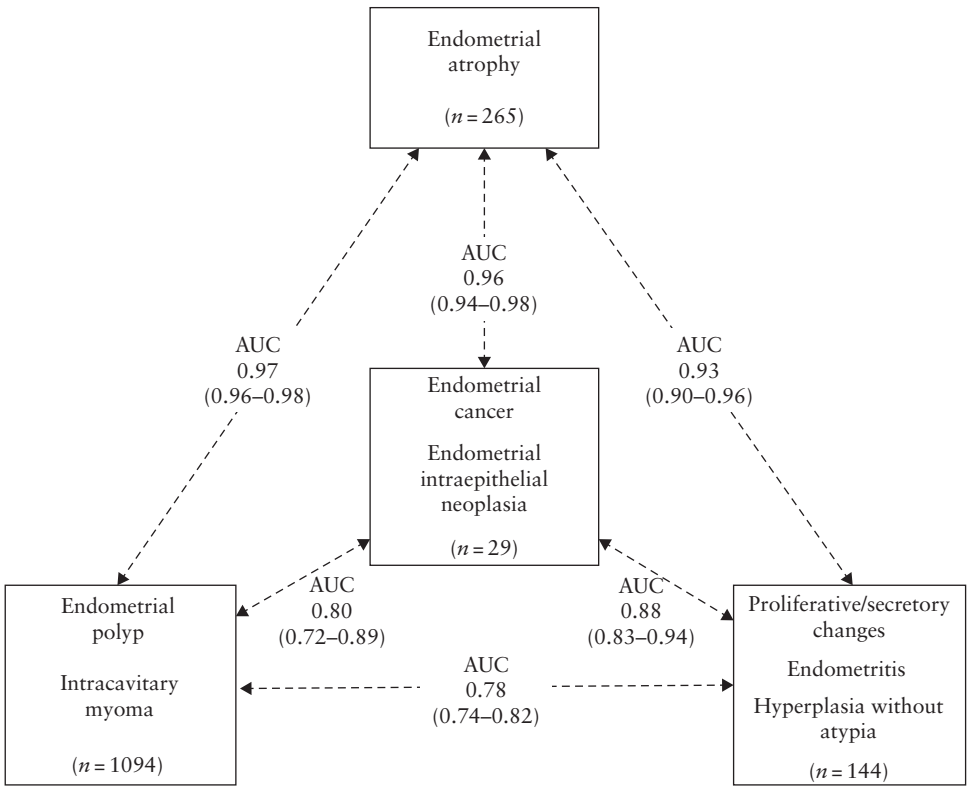

Figure 3 Diagram illustrating International Endometrial Tumor Analysis (IETA)-1 model's ability to distinguish between four histological outcome categories, illustrated by pairwise areas under the receiver-operating-characteristics curves (AUC) with 95% CIs.

of 0.81 (95% CI, 0.71–0.91) while endometrial thickness alone gave an AUC of 0.70 (95% CI, 0.60–0.81) (difference in AUC, 0.11; 95% CI, 0.01–0.20).

The sensitivity, specificity, accuracy, LR+ and LR– of the IETA-1 model in distinguishing EC or EIN from benign outcomes at different risk thresholds and at different endometrial thickness thresholds are shown in Tables 1 and 2 (all cases) and in Tables S4 and S5 (only histologically confirmed cases). The results were similar, irrespective of whether all women or only those with a histological outcome were included. For the entire cohort of 1745 women, at a ≥ 1% risk of malignancy, the model showed a sensitivity of 100% and specificity of 34.7%. At a ≥ 20% risk of malignancy, the model's sensitivity was 31.0% and specificity was 98.2% (Table 1). An endometrial thickness ≥ 3 mm predicted malignancy with a sensitivity of 100% and specificity of 11.4%, and an endometrial thickness ≥ 11 mm had a sensitivity of 55.6% and specificity of 67.1% (Table 2).

DISCUSSION

This is the first study to evaluate the performance of the IETA-1 prediction model in women without abnormal vaginal bleeding. The model discriminated better between EC or EIN and benign histology than did endometrial thickness alone in asymptomatic women, and it was very successful in discriminating between endometrial atrophy and all other intracavitary uterine conditions. It was well-calibrated for endometrial polyps or intracavitary myomas, slightly overestimated endometrial atrophy and substantially overestimated the risk of malignancy as well as the likelihood of proliferative or secretory endometrial changes, endometritis, or hyperplasia without atypia.

The IETA-3 study is the largest study to date relating ultrasound characteristics to different endometrial pathologies in women without abnormal bleeding using standardized terminology. Our intention was to include patients recruited consecutively. Therefore, centers that contributed fewer than 50 women to the study were excluded. However, the distribution of histological diagnoses, for example the high prevalence of polyps and intracavitary myomas, suggests that our study sample may still be a convenience series affected by selection bias. Therefore, our results might not be completely generalizable to all asymptomatic women. It is also a limitation that not all patients had a diagnosis based on histology. To minimize selection bias caused by exclusion of patients without histology, we classified the outcome as benign in 208 patients (12% of our sample size) without histology but with no clinical or sonographic signs of malignancy at follow-up at 1 year of age or later (differential verification bias). Another limitation is the use of blind endometrial sampling in a small proportion of cases (100/1745 (6%)), which may have resulted in some focal pathology, such as polyps, being missed[3]. However, we believe that this would not significantly bias the results related to the primary aim of the study, which was to separate benign from malignant intracavitary pathology. Another limitation is the small number of EC and EIN cases, resulting in wide confidence intervals around the AUC to distinguish EC and EIN from benign conditions and around the observed/expected ratio for EC and EIN. Because of the clinical importance of an incidental finding of EC or EIN,

Table 1 Diagnostic accuracy of International Endometrial Tumor Analysis (IETA)-1 mathematical model to discriminate between endometrial cancer or endometrial intraepithelial neoplasia and benign endometrium* in 1745 women without abnormal vaginal bleeding

Risk	*Sensitivity*	*Specificity*	*Accuracy*	*LR+*	*LR–*	*At or above risk threshold*
≥ 1%	29/29 (100)	596/1716 (34.7)	625/1745 (35.8)	1.53	< 0.001	1149/1745 (65.8)
≥ 2%	22/29 (75.9)	1098/1716 (64.0)	1120/1745 (64.2)	2.11	0.38	640/1745 (36.7)
≥ 3%	21/29 (72.4)	1307/1716 (76.2)	1328/1745 (76.1)	3.04	0.36	430/1745 (24.6)
≥ 4%	17/29 (58.6)	1405/1716 (81.9)	1422/1745 (81.5)	3.24	0.51	328/1745 (18.8)
≥ 5%	17/29 (58.6)	1479/1716 (86.2)	1496/1745 (85.7)	4.24	0.48	254/1745 (14.6)
≥ 10%	13/29 (44.8)	1620/1716 (94.4)	1633/1745 (93.6)	8.01	0.58	109/1745 (6.2)
≥ 20%	9/29 (31.0)	1685/1716 (98.2)	1694/1745 (97.1)	17.18	0.70	40/1745 (2.3)

Data are presented as *n*/*N* (%), unless stated otherwise. *Irrespective of whether outcome was based on histological diagnosis or on follow-up. LR+, positive likelihood ratio; LR–, negative likelihood ratio.

Table 2 Diagnostic accuracy of endometrial thickness, when measurable ($n = 1689$), to discriminate between endometrial cancer or endometrial intraepithelial neoplasia and benign endometrium* in women without abnormal vaginal bleeding

Endometrial thickness	*Sensitivity*	*Specificity*	*Accuracy*	*LR+*	*LR–*	*At or above endometrial thickness threshold*
≥ 3 mm	27/27 (100)	189/1662 (11.4)	216/1689 (12.8)	1.13	< 0.001	1499/1689 (88.8)
≥ 4 mm	26/27 (96.3)	252/1662 (15.2)	278/1689 (16.5)	1.14	0.24	1435/1689 (85.0)
≥ 5 mm	26/27 (96.3)	318/1662 (19.1)	344/1689 (20.4)	1.19	0.19	1369/1689 (81.1)
≥ 8 mm	19/27 (70.4)	697/1662 (41.9)	716/1689 (42.4)	1.21	0.70	983/1689 (58.2)
≥ 11 mm	15/27 (55.6)	1116/1662 (67.1)	1131/1689 (67.0)	1.69	0.66	560/1689 (33.2)

Data are presented as *n*/*N* (%), unless stated otherwise. *Irrespective of whether outcome was based on histological diagnosis or on follow-up. LR+, positive likelihood ratio; LR–, negative likelihood ratio.

we find it relevant to report these results despite the AUC and observed/expected estimates being imprecise.

The IETA-1 model provided better discrimination between benign and malignant conditions in symptomatic women (IETA-1 population), for whom it was initially constructed, than it did in the IETA-3 cohort of asymptomatic women, with an AUC of 0.88 (95% CI, 0.85–0.91)[7] compared with 0.81 (95% CI, 0.73–0.89). Surprisingly, however, the IETA-1 model performed slightly better in the asymptomatic IETA-3 cohort than it did in the symptomatic IETA-1 cohort for discrimination between the benign outcome categories: pairwise AUCs for atrophy *vs* polyps or myomas were 0.97 (95% CI, 0.96–0.98) and 0.88 (95% CI, 0.87–0.90), respectively, those for atrophy *vs* proliferative or secretory endometrium, endometritis, or endometrial hyperplasia without atypia were 0.93 (95% CI, 0.90–0.96) and 0.87 (95% CI, 0.85–0.89), respectively, and those for polyps or myomas *vs* proliferative or secretory endometrium, endometritis, or endometrial hyperplasia without atypia were 0.78 (95% CI, 0.74–0.82) and 0.76 (95% CI, 0.74–0.79), respectively. Hence, the PDI in the present study was marginally better than that in the IETA-1 study: 0.68 (95% CI, 0.62–0.73) *vs* 0.67 (95% CI, 0.63–0.75). These results suggest that, when the decision has been made to investigate a patient's endometrium further, with ultrasound, it is worth considering using the IETA-1 model in asymptomatic as well as in symptomatic women. However, using the model exposes asymptomatic women to the risk of overtesting and overtreatment, albeit to a lesser extent than if using endometrial thickness alone.

For the past decade, endometrial thickness has been the prime focus of risk assessment of EC in asymptomatic, postmenopausal women. Based on theoretical reasoning, Smith-Bindman *et al.*[11] proposed a lower threshold for endometrial thickness of 11 mm to initiate investigations to exclude malignancy in asymptomatic postmenopausal women. Several studies support the 11-mm threshold[12–14]. Others have suggested endometrial thresholds ranging from 3 mm to 15 mm to initiate further testing[15–20], while still others advocate against the use of endometrial thickness alone as a decision-making tool[21–23].

Both the current study and the IETA-1 model development study[7] illustrate that the risk of endometrial malignancy is related not only to endometrial thickness, but also to other sonographic features. The IETA-1 model could potentially be of help when deciding whether and how to proceed with further testing in case of an incidental finding of 'thickened' endometrium in a postmenopausal woman, or in case of an ambiguous endometrial ultrasound image in an asymptomatic premenopausal woman (in whom endometrial thickness alone is seldom the single determining factor for further work-up). However, it is important to emphasize that, at present, there is no evidence of any survival advantage of diagnosing asymptomatic EC[24,25] and that, therefore, screening for EC is not recommended[26].

We conclude that the multivariable IETA-1 model discriminates well between intracavitary pathologies in women without abnormal vaginal bleeding and that it outperforms endometrial thickness alone for discrimination between endometrial malignancy and benign intracavitary conditions. The model can help clinicians with patient counseling if they detect incidentally that the endometrium appears abnormal on ultrasound in an asymptomatic woman. However, clinicians need to keep in mind that the model overestimates the risk of malignancy in asymptomatic women.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Model intercepts and regression coefficients to calculate likelihood of four histological outcome categories[7]

Table S2 Comparison of model predictors between validation data (International Endometrial Tumor Analysis (IETA)-3[3] patient cohort) and development data (IETA-1[4,7] patient cohort) for the total cohorts and for women with histological outcome

Table S3 Comparison of model predictors between validation data (International Endometrial Tumor Analysis (IETA)-3[3] patient cohort) and development data (IETA-1[4,7] patient cohort) for women without histological confirmation

Table S4 Diagnostic accuracy of International Endometrial Tumor Analysis (IETA)-1 mathematical model to discriminate between endometrial cancer or endometrial intraepithelial neoplasia and benign endometrium in women without abnormal vaginal bleeding (histologically confirmed cases only, $n = 1537$)

Table S5 Diagnostic accuracy of endometrial thickness, when measurable, to discriminate between endometrial cancer or endometrial intraepithelial neoplasia and benign endometrium in women without abnormal vaginal bleeding (histologically confirmed cases only, $n = 1487$)

Appendix S1 Examples illustrating use of International Endometrial Tumor Analysis (IETA)-1 model and required transformations

Appendix S2 Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) checklist[10]

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Estimación del riesgo de cáncer de endometrio y otras patologías uterinas intracavitarias en mujeres sin hemorragia uterina anómala mediante el modelo de regresión multinomial IETA-1: estudio de validación

RESUMEN

Objetivos. Evaluar la capacidad del modelo de regresión polinómica del Análisis Internacional de Tumores Endometriales (IETA)-1 para estimar el riesgo de cáncer de endometrio (CE) y otras patologías uterinas intracavitarias en mujeres sin hemorragia uterina anómala.

Métodos. Se trata de un estudio retrospectivo en el que validamos el modelo IETA-1 en la cohorte de estudio IETA-3 (n=1745). El estudio IETA-3 es un estudio multicéntrico observacional prospectivo. Incluye a mujeres sin sangrado vaginal que se sometieron a una ecografía transvaginal estandarizada en uno un centro de ecografía de un total de siete entre enero de 2011 y diciembre de 2018. La ecografía se realizó como parte de un examen ginecológico rutinario, durante el seguimiento de una patología no endometrial, como parte de una exploración antes de someterse a un tratamiento de fertilidad, o antes de un tratamiento de prolapso uterino o patología ovárica. Los hallazgos ecográficos se describieron utilizando la terminología de la IETA y se compararon con la histología, o con los resultados de un seguimiento clínico y ecográfico de al menos 1 año si no se había realizado un muestreo endometrial. El modelo IETA-1, creado a partir de datos de pacientes con hemorragia uterina anómala, predice cuatro resultados histológicos: (1) CE o neoplasia intraepitelial endometrial (NIE); (2) pólipo endometrial o mioma intracavitario; (3) endometrio proliferativo o secretor, endometritis o hiperplasia endometrial sin atipia; y (4) atrofia endometrial. Los predictores del modelo son la edad, el índice de masa corporal y siete variables ecográficas (visibilidad del endometrio, grosor endometrial, puntuación de color, quistes en el endometrio, ecogenicidad no uniforme del endometrio, presencia de un borde brillante, presencia de un único vaso dominante). Se analizó la capacidad discriminativa del modelo (área bajo la curva de características operativas del receptor [ABC]; índice de discriminación politómica [IDP]) y se evaluó la calibración de sus estimaciones de riesgo (cociente observado/esperado).

Resultados. La edad media de las mujeres de la cohorte IETA-3 era de 51 años (rango, 20–85) y el 51% (887/1745) de las mujeres eran posmenopáusicas. La histología mostró la presencia de CE y/o NIE en 29 (2%) mujeres, pólipos endometriales o miomas intracavitarios en 1094 (63%) mujeres, endometrio proliferativo o secretor, endometritis o hiperplasia sin atipia en 144 (8%) mujeres, y atrofia endometrial en 265 (15%) mujeres. La muestra de endometrio no tenía material suficiente en cinco (0,3%) casos. El resultado se clasificó como benigno en las 208 (12%) mujeres que no se sometieron a un muestreo endometrial, pero a las que se les dio seguimiento durante al menos 1 año sin indicios clínicos o ecográficos de malignidad endometrial. El modelo IETA-1 tuvo un ABC de 0,81 (IC 95%, 0,73–0,89; n=1745) para la discriminación entre endometrio maligno (CE o NIE) y benigno, y el cociente observado/esperado para el CE o la NIE fue de 0,51 (IC 95%, 0,32–0,82). El modelo fue capaz de clasificar los cuatro resultados histológicos con una precisión considerable: el IDP del modelo fue de 0,68 (IC 95%, 0,62–0,73) (n=1532). El modelo IETA-1 discriminó muy bien entre la atrofia endometrial y todas las demás afecciones uterinas intracavitarias, con un ABC de 0,96 (IC 95%, 0,95–0,98). Si se incluyen únicamente a las pacientes en las que el endometrio era medible (n=1689), el ABC del modelo fue de 0,83 (IC 95%, 0,75–0,91), frente a 0,62 (IC 95%, 0,52–0,73) cuando se utilizó únicamente el grosor endometrial para predecir la malignidad (diferencia en el ABC, 0,21; IC 95%, 0,08–0,32). En mujeres posmenopáusicas con grosor endometrial medible (n=848), el modelo IETA-1 dio un ABC de 0,81 (IC 95%, 0,71–0,91), mientras que el grosor endometrial por sí solo dio un ABC de 0,70 (IC 95%, 0,60–0,81) (diferencia en el ABC, 0,11; IC 95%, 0,01–0,20).

Conclusión. El modelo IETA-1 discrimina bien entre condiciones benignas y malignas en la cavidad uterina en pacientes sin sangrado anómalo, pero sobrestima el riesgo de malignidad. También discrimina bien entre las cuatro categorías histológicas de resultados.

利用 IETA-1 多项式回归模型估算无异常子宫出血妇女患子宫内膜恶性肿瘤及其他腔内子宫病变的风险：验证研究

摘要

目的 评估国际子宫内膜肿瘤分析（IETA）-1多项式回归模型估算无异常子宫出血妇女患子宫内膜癌（EC）和其他腔内子宫病变风险的能力。

方法 这是一项回顾性研究，我们在 IETA-3 研究队列（n=1745）中验证了 IETA-1 模型。该 IETA-3 研究是一项前瞻性多中心观察研究。研究对象包括 2011 年 1 月至 2018 年 12 月期间在七个超声中心之一接受标准化经阴道超声检查的无阴道出血妇女。行超声检查的四种情形为：常规妇科检查、非子宫内膜病变随访、生育治疗前的病性检查、子宫脱垂或卵巢病变治疗前的检查。超声检查结果使用 IETA 术语进行描述，并与组织学结果进行比较，如果未进行子宫内膜取样，则与至少 1 年的临床和超声随访结果进行比较。IETA-1 模型利用异常子宫出血患者的数据搭建，可预测四种组织学结果：（1）EC 或子宫内膜上皮内瘤变（EIN）；（2）子宫内膜息肉或腔内肌瘤；（3）增殖期或分泌期子宫内膜、子宫内膜炎或无不典型性的子宫内膜增生；以及（4）子宫内膜萎缩。模型中的预测因素包括年龄、体重指数和七个超声变量（子宫内膜能见度、子宫内膜厚度、颜色评分、子宫内膜囊肿、子宫内膜回声不均匀、存在明亮边缘、存在单一优势血管）。我们分析了模型的分辨能力（接受者操作特性曲线下面积（AUC）和多类别辨别指数（PDI），并评估了其风险估计值的校准（观察/预期比）。

结果 IETA-3 队列中妇女的中位年龄为 51 岁（20-85 岁），51%（887/1745）已绝经。组织学检查结果显示，29（2%）名妇女患有 EC 或 EIN，1094（63%）名妇女患有子宫内膜息肉或腔内肌瘤，144（8%）名妇女患有增殖期或分泌期子宫内膜、子宫内膜炎或无不典型性增生，265（15%）名妇女患有子宫内膜萎缩。5 例（0.3%）子宫内膜样本材料不足。在 208 例（12%）未进行子宫内膜取样但随访至少 1 年且无子宫内膜恶性肿瘤临床或超声征象的妇女中，结果被归类为良性。IETA-1 模型在区分恶性（EC 或 EIN）和良性子宫内膜肿瘤方面的 AUC 为 0.81（95% CI，0.73-0.89，n=1745），EC 或 EIN 的观察/预期比为 0.51（95% CI，0.32-0.82）。该模型能够相当准确地对四种组织学结果进行分类：PDI 为 0.68（95% CI，0.62-0.73）（n=1532）。IETA-1 模型能很好地区分子宫内膜萎缩和所有其他腔内子宫病症，其 AUC 为 0.96（95% CI，0.95-0.98）。如果只包括子宫内膜可测量的患者（1689 人），该模型的 AUC 为 0.83（95% CI，0.75-0.91），而如果只使用子宫内膜厚度，则预测恶性肿瘤的 AUC 为 0.62（95% CI，0.52-0.73）（AUC 差为 0.21；95% CI，0.08-0.32）。在可测得子宫内膜厚度的绝经妇女（848 人）中，IETA-1 模型的 AUC 为 0.81（95% CI，0.71-0.91），而如果只使用子宫内膜厚度，则 AUC 为 0.70（95% CI，0.60-0.81）（AUC 差为 0.11；95% CI，0.01-0.20）。

结论 IETA-1 模型能很好地区分无异常出血患者子宫腔内的良性和恶性病变，但会高估恶性肿瘤的风险。该模型还能很好地区分四种组织学结果类别。

