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Original Research

Prospective validation of two mathematical models to calculate the risk of endometrial malignancy in patients with postmenopausal bleeding and sonographic endometrial thickness ≥4.5 mm☆

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Abstract ***Aim:*** To prospectively validate two mathematical models for calculating the likelihood of endometrial malignancy in patients with postmenopausal bleeding (PMPB), sonographic endometrial thickness (ET) ≥4.5 mm and no fluid in the uterine cavity.
Methods: This is a prospective observational diagnostic validation study performed in a PMPB clinic in a university hospital. Of 860 consecutive patients, 350 fulfilled our inclusion criteria. A standardized history was taken, clinical and transvaginal grey scale and power Doppler ultrasound examinations were performed following a research protocol. The percentage vascularized area of the endometrium at power Doppler examination (VI) was calculated using computer software. The colour content of the endometrial scan was estimated subjectively on a visual analogue scale (VAS). Gold standard was the histological diagnosis of the endometrium. Main outcome measures were area under the receiver operating characteristic curve (AUC), sensitivity and specificity when using the cut-offs suggested in the original study, and calibration curves.
Results: Eighty (23%) patients had malignant endometrium. The performance of the models was similar to that in the original study. The model including patient's age, use of hormone therapy, ET and VAS performed best (AUC 0.91; 95% confidence interval [CI] 0.87–0.95; sensitivity 70%, specificity 93%). The model including ET, VI, patient's age and hormone

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therapy use had AUC 0.89 (95% CI 0.84–0.93; sensitivity 79%; specificity 81%). ET had AUC 0.83 (95% CI 0.78–0.88). The models were reasonably well calibrated.
Conclusion: On prospective validation both models retained their diagnostic performance. This suggests that they are robust and potentially clinically useful for individualized patient management.

1. Introduction

Endometrial thickness (ET) as measured with transvaginal ultrasound can be used to categorize patients with postmenopausal bleeding (PMPB) into a low risk group and high risk group with regard to endometrial malignancy. Patients with sonographically "thin" endometrium (the definition in the literature ranges from ≤2.9 to ≤4.9 mm [1,2]) have a low risk of endometrial malignancy. Patients with sonographically "thick" endometrium (the definition in the literature ranges from ≥3 to ≥5.0 mm [1,2]) have a higher risk of endometrial malignancy, and the thicker the endometrium the higher the risk [3–5]. Heterogeneous endometrium at grey scale ultrasound examination and high colour content or abnormal endometrial vessels at power Doppler ultrasound further increase the risk of endometrial malignancy in patients with thick endometrium [3–5]. Clinical factors also affect the risk [6,7]. We have created logistic regression models including clinical, grey scale and colour Doppler ultrasound variables to calculate the likelihood of endometrial malignancy in patients with PMPB, sonographic ET ≥ 4.5 mm and no fluid in the uterine cavity [5]. The arguments for creating models only for patients with ET ≥ 4.5 mm and without fluid in the uterine cavity are the following. A risk calculation model for patients with PMPB and "thin" ET (<3–5 mm) is of limited clinical value because the likelihood of endometrial malignancy is small in these patients and many believe that patients with thin endometrium can be safely dismissed without endometrial sampling [1,8,9]. Irregular surface of the endometrium or of a lesion in a fluid filled uterine cavity entails a very high risk of malignancy, so that information on endometrial echogenicity or vascularity adds little to diagnosis [10]. Moreover, the colour Doppler image of the endometrium differs depending on whether there is fluid in the uterine cavity or not [11]. This means that separate models would need to be developed for patients with and without fluid in the uterine cavity. Two models (mathematical formulas shown in Table 1) performed well in our original study [5]. However, before introducing any models into clinical practice they need to be prospectively validated [12]. Without validation one cannot know if a model performs equally well when applied on other patients and when used by other staff than those in the study in which the model was created.

The aim of this study was to prospectively validate the diagnostic performance of the two logistic regression models described in Table 1 when they were applied on the specific subgroup of patients for which they were created.

2. Patients and methods

The Ethics Committee of Lund University approved the study protocol. Informed consent was obtained from all participants after the nature of the procedures had been fully explained to them.

This is a prospective temporal diagnostic validation study. The patients included in the study were recruited from the PMPB clinic, Department of Obstetrics and Gynaecology, Skåne University Hospital, Malmö, Sweden. Recruitment was between 1st June 2009 and 15th March 2014. The definition of postmenopause was absence of vaginal bleeding for at least 1 year after the age of 40 years provided that the amenorrhoea was not explained by medication or disease. PMPB was defined as any vaginal bleeding in a postmenopausal woman not using hormone replacement therapy (HRT), or

Table 1
The mathematical formulas for the two multivariate logistic regression models [5] for prediction of endometrial malignancy undergoing temporal validation.

z in the mathematical formulas
Model A
−6.693 + (0.044 × patient's age in years) − (1.187 × use of hormone replacement therapy; coded 1 if used and 0 if not used) + (0.058 × endometrial thickness in mm) + (0.056 × colour content of the endometrial scan at power Doppler ultrasound examination as estimated subjectively on a visual analogue scale graded from 0 to 100)
Model B
−9.356 + (0.069 × patient's age in years) − (1.333 × use of hormone replacement therapy; coded 1 if used and 0 if not used) + (0.084 × endometrial thickness in mm) + (0.088 × vascularity index in percent)

Risk is calculated as $[e^z/(1 + e^z)]$ and z is presented in the table. $e = 2.718$ (base value of natural logarithms).