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Original Article

Histopathology of women with non-uniform endometrial echogenicity and risk factors for atypical endometrial hyperplasia and carcinoma

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Abstract: Objective: In sonography, homogeneous endometrium is defined as uniform endometrial echogenicity and heterogeneous, asymmetrical or cystic endometrium is defined as non-uniform. However, the relationship between the non-uniform endometrial echogenicity and the presence or absence of pathology is not known. A retrospective study of the patients with ultrasound non-uniform endometrium who underwent hysteroscopy-directed biopsy was performed to explore its clinical meaning in the diagnosis of endometrial lesions. Materials and methods: Patients with non-uniform endometrial echogenicity who underwent hysteroscopy-directed biopsy were enrolled in the Obstetrics and Gynecology Hospital of Fudan University from January 2015 to May 2018 as the primary cohort. In total, 692 patients with non-uniform endometrial echogenicity were diagnosed and underwent hysteroscopy-directed biopsy. Characteristics were assessed using univariate logistic regression between patients with and without atypical endometrial hyperplasia and carcinoma (atypical EH+). Multivariate analyses were used to develop the predicting model. We incorporated statistically significant variables and presented with nomogram. Internal validation was assessed. An independent validation cohort consisted of 237 consecutive patients from June 2018 to February 2019. Results: Hysteroscopy-directed biopsy showed that 55.20% (382/692) of the patients with non-uniform endometrium had normal endometrium, while 44.80% (310/692) had endometrial lesions, including 39.31% (272/692) benign lesions and 5.49% (38/692) atypical EH+. Univariate logistic analysis showed that older age (P=0.027), abnormal uterine bleeding (AUB) before menopause (P=0.011), postmenopausal bleeding (P<0.001) and endometrial thickness ≥7 mm (P=0.013) were statistically significant for atypical EH+. Multivariate logistic regression analysis showed that age ≥50 years old (OR: 3.97, 95% CI: 1.17-13.43, P=0.027), endometrial thickness ≥7 mm (OR: 8.08, 95% CI: 1.86-35.08, P=0.005) and postmenopausal bleeding (OR: 8.98, 95% CI: 3.26-24.76, P<0.001) were risk factors for atypical EH+. Predictors in the individualized predicted nomogram included age ≥50 years old, AUB before menopause, postmenopausal bleeding and endometrial thickness ≥7 mm. The model showed good discrimination with area under curve (AUC) of 77.09%. With cutoff value of 0.0089267, the recall of atypical EH+ is 100% with precision 6.52% and 6.22% in both primary and validation cohort, respectively. Conclusion Non-uniform endometrial echogenicity is clinically meaningful in assessment of atypical EH+ with risk factors of age ≥50 years old, postmenopausal bleeding and endometrial thickness ≥7 mm. The model can help clinician to predicate the probability of atypical EH+ and make clinical decision.

Keywords: Non-uniform endometrium, echogenicity, hysteroscopy, histopathology, risk factors, atypical endometrial hyperplasia, endometrial carcinoma, endometrial lesions

Introduction

Uterine cancer is the most common gynecologic malignancy in developed countries and is the second most common cancer of the female reproductive system with the increasing trend worldwide (4.4% of cancers in women) [1-3]. Endometrial carcinoma is the most common histologic site and type of uterine cancer. Transvaginal sonography (TVS) is a non-invasive, cost-effective technique in detecting intrauterine lesions and widely used in routine practice for the diagnosis and follow-up of women with endometrial lesions [4]. Ultrasonographic

findings of endometrial carcinoma focus on the intracavitary lesions and endometrial thickness [5-8]. However, TVS sometimes showed non-uniform endometrium without indicating intracavitary lesions.

An evaluation of endometrial morphology includes an assessment of endometrial echogenicity, the endometrial midline and the endometrial-myometrial junction [9]. According to the consensus opinion about the endometrium and intrauterine lesions from the International Endometrial Tumor Analysis (IETA) group [9], endometrial echogenicity was defined as uniform if the endometrium is homogeneous and with symmetrical anterior and posterior sides. A uniform endometrium includes the three-layer pattern, as well as the homogeneous hyperechogenic, hypoechogenic and isoechogenic endometrium. The echogenicity is defined as non-uniform if the endometrium appears heterogeneous, asymmetrical or cystic. Uniform vs non-uniform echogenicity was the grayscale ultrasound variable with the best reliability, and endometrial-myometrial junction and the nine-category endometrial echogenicity variable with the lowest reliability [10]. Hence, uniform/non-uniform echogenicity is suitable for endometrial assessment worldwide. Endometrium should be uniform in thickness, homogeneous in echotexture, and not displaced by any submucosal, myometrial abnormality [11-14]. Clinically, uniform echogenicity in sonography indicates normal endometrium. However, the relationship between the non-uniform endometrial echogenicity and the presence or absence of pathology is not known. In endometrioid tumors, it was shown that tumors were less likely to have uniform echogenicity with increasing grade and stage [15]. A few studies have found high predictive values for heterogeneous endometrium [16, 17], however, there is no study focusing on the clinical meaning of non-uniform endometrial echogenicity without intracavitary lesions yet.

Hysteroscopy-directed biopsy is the gold standard for diagnosis of endometrial lesions and yields higher accuracy than blind dilation and curettage [18-20]. Hence, we retrospectively analyzed histopathology and clinical features of women with non-uniform endometrial echogenicity to explore the clinical meaning of non-uniform endometrial echogenicity in the diagnosis of endometrial lesions.

Materials and methods

Study type and patient population

Approval was obtained from institutional review board of the Obstetrics and Gynecology Hospital of Fudan University before data collection. A retrospective computer-based search was performed. Digital medical records were collected from the database of the hospital. Patients with non-uniform endometrial echogenicity who underwent hysteroscopy-directed biopsy were enrolled from January 2015 to May 2018 as the primary cohort. An independent validation cohort was enrolled from June 2018 to February 2019.

The histopathology and clinical features of women, including age at the time of diagnosis, clinical manifestations, menopausal status, comorbidity including diabetes, hypertension and hyperthyroidism, gravidity, were collected. Clinical manifestations consist of postmenopausal bleeding, AUB before menopause and health check-ups. AUB before menopause included abnormal frequency, duration, regularity and flow volume, intermenstrual bleeding in non-gravid women of reproductive age. Inclusion criteria: women with non-uniform endometrial echogenicity diagnosed by TVS who underwent hysteroscopy-directed biopsy and obtained according histopathology reports (**Figure 1**). Exclusion criteria: (1) women with intracavitary lesions diagnosed by TVS; (2) women with treatment of tamoxifen or hormone. All pathologic specimens were processed by a standardized protocol, interpreted by an experienced staff pathologist, and then verified by another advanced pathologist.

Ultrasound equipment

Ultrasonography was performed by ultrasonologists with over 10 years of work experience using high-performance ultrasound equipment. The patients underwent at least two ultrasonic examinations with different experienced doctors, and the results were cross checked. Standard transvaginal ultrasonographic examinations were performed using a Voluson 730 Expert or Voluson E8 system (GE Healthcare Ultrasound, Milwaukee, WI, USA) with the RIC 5-9H transvaginal probe, DU8, my lab70 system (Esaote, Ultrasound, SpA, Genoa, Italy) with the SE3133 transvaginal probe, or HD11_

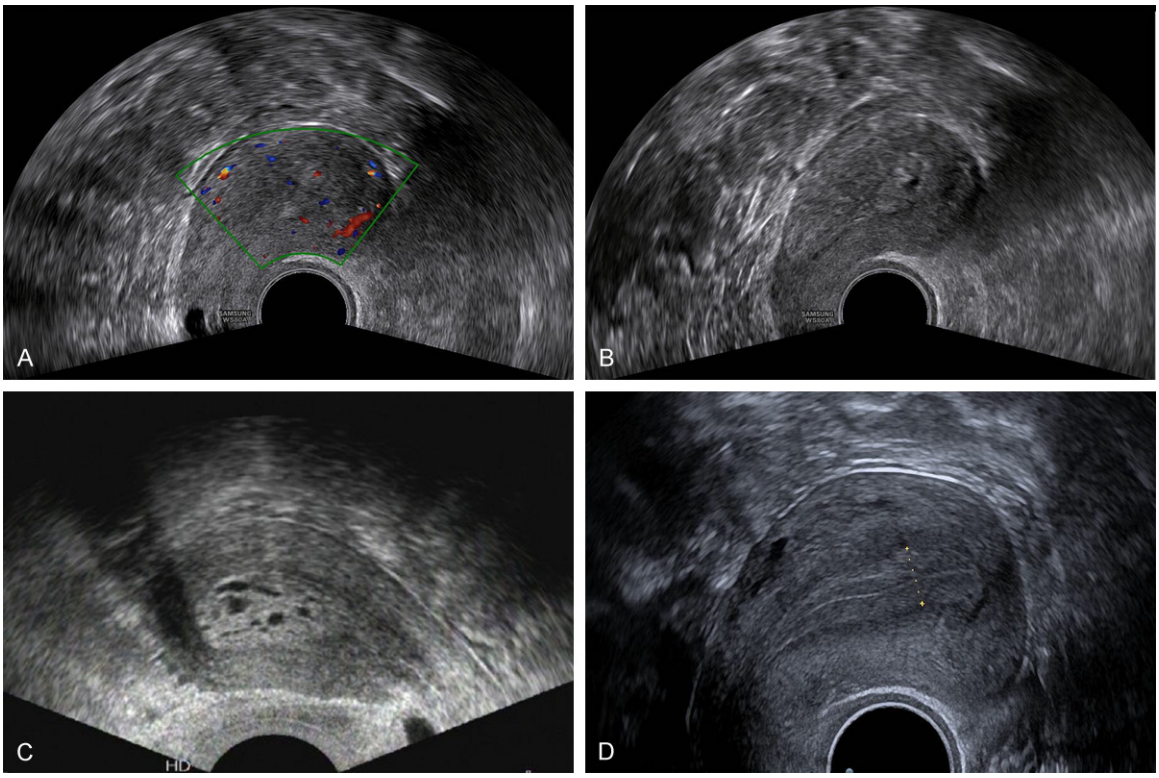

Figure 1. Ultrasound image of non-uniform and uniform endometrial echogenicity. A-C. Showed non-uniform echogenicity with heterogeneous, asymmetrical or cystic endometrium in ultrasonography. D. Showed uniform echogenicity with homogeneous endometrium in ultrasonography.

XE system (Philip Ultrasound, Bothell, WA, USA) with the C8-4v transvaginal probe.

Statistical analysis

The results of the descriptive analysis of qualitative variables were expressed as frequencies and percentages, and quantitative variables were expressed as medians, or means with standard deviation. Endometrial cancer is primarily a disease affecting post-menopausal women [21]. Recently, it has been estimated that 5%~30% of cases of cancer occur in women under 50 years of age [22]. As previous studies of endometrial cancer have focused on younger women (younger than 50 years old) [23, 24] or post-menopausal women [21], 50 years old is set as the cutoff in this study. Besides, it is often the cutoff in other cancer screening programs for younger and older groups [25, 26]. The endometrial thickness less than 5 mm using TVS is a common method of excluding women with endometrial lesions in postmenopausal women [27]. However, we didn't choose it as our criteria. We checked 38 patients with atypical EH+ and found only 2 endometrial thickness were less than 7 mm with 3 mm and 4 mm, respectively. Hence, we set the endometrial thickness cutoff of 7 mm, and divided women of all ages into <7 mm and ≥7 mm group. Characteristics including age, clinical manifestations, menopausal status, comorbidity, gravidity, endometrial thickness were assessed using univariate logistic regression between patients with and without endometrial atypical EH+. Clinically meaningful predictors were included in multiple logistic regression model with the method of entry to develop the predicting model. Receiver operating characteristic (ROC) curve was drawn. The nomogram was developed. Internal validation was assessed. Recall and precision in both the primary cohort and validation cohort was calculated. TP, FP and FN are the acronyms of true positive, false negative and false negative, respectively. Recall was calculated as TP/(TP+FN) %. Precision was calculated as TP/(TP+FP) %. A p-value <0.05 was considered statistically significant. Statistical analyses were

Table 1. Histopathological results of hysteroscopy-directed biopsy in 692 patients with non-uniform endometrial echogenicity

Histopathological results	n	percent
Normal endometrium	382	55.20%
Proliferative or secretory phases or postmenopausal endometrium	382	55.20%
Endometrial lesions	310	44.80%
Benign lesions without hyperplasia	230	33.24%
Polyps	214	30.92%
Disordered proliferation	10	1.45%
Degenerative placenta	6	0.87%
Endometrial hyperplasia(EH)	56	8.09%
EH without atypia	42	6.07%
EH with atypia	14	2.02%
Carcinoma	24	3.47%
Endometrioid adenocarcinoma	18	2.60%
Mixed adenocarcinoma	2	0.29%
Carcinosarcoma	2	0.29%
Adenosarcoma	2	0.29%
Total	692	100.00%

performed using Stata15.1 (StataCorp LLC, Texas, USA).

Results

Histopathological results of hysteroscopy-directed biopsy in patients with non-uniform endometrium

A total of 692 patients were enrolled in the primary cohort (n=692). Hysteroscopy-directed biopsy showed that 55.20% (382/692) of the patients with non-uniform endometrium were diagnosed with normal endometrium, while 44.80% (310/692) were with endometrial lesions, including benign lesions without hyperplasia (33.24%, 230/692), hyperplasia without atypia (6.07%, 42/692), atypical hyperplasia (2.02%, 14/692) and malignancy (3.47%, 24/692). Benign lesions without hyperplasia were made up of endometrial polyps, disordered proliferation and degenerative placenta. Endometrial hyperplasia without atypia included simple hyperplasia and complex hyperplasia. Malignancy included endometrial carcinomas (endometrioid adenocarcinoma, mixed adenocarcinoma and carcinosarcoma) and sarcoma (adenosarcoma). Detailed histopathological results and distribution are shown in **Table 1**.

A total of 5.49% (38/692) women were diagnosed with atypical EH+. Among them, 36.84% (14/38) complained of postmenopausal vaginal bleeding, 34.21% (13/38) complained of AUB before menopause, and 28.95% (11/38) were found accidentally in health check-ups. A total of 39.31% (272/692) of women were diagnosed with benign lesions of the endometrium, including degenerative placenta, polyps, non-atypical simple hyperplasia and non-atypical complex hyperplasia. Among them, 11.03% (30/272) complained of postmenopausal vaginal bleeding, 22.43% (61/272) complained of AUB before menopause, and 66.54% (181/272) were found accidentally in health check-ups.

Characteristics assessed using univariate logistic regression between patients with and without endometrial atypical EH+

Older age (55.71±14.45 VS 48.41±14.15, P=0.027), AUB before menopause (P=0.011), postmenopausal bleeding (P<0.001) and endometrial thickness ≥7 mm (P=0.013) were statistically significant for atypical EH+ by univariate logistic regression. Other variables including menopause, comorbidity and gravidity were not statistically significant in patients with non-uniform endometrium (**Table 2**).

Multivariate logistic regression analysis of risk factors of endometrial lesions in patients with non-uniform endometrium

Candidate predictors (comorbidity, menopause, age ≥50 years old, AUB before menopause,

Table 2. Univariate logistic regression for risk factors of atypical EH+ in patients with non-uniform endometrium

Characteristics	Endometrium without atypical hyperplasia and carcinoma n=654 (94.51%)	Endometrium with atypical hyperplasia and carcinoma n=38 (5.49%)	OR (95% CI)	*P*-value
Age, mean ± SD, years	48.41±14.15	55.71±14.45	1.03 (1.00-1.05)	0.027*
Age, years				
<50	340 (51.99%)	14 (36.84%)	ref	
≥50	314 (48.01%)	24 (63.16%)	1.86 (0.94-3.65)	0.073
Menopausal status				
Premenopause	284 (43.43%)	20 (52.63%)	ref	
Postmenopause	370 (56.57%)	18 (47.37%)	0.69 (0.36-1.33)	0.269
Medical comorbidities				
No	330 (86.39%)	261 (84.19%)	ref	
Yes	52 (13.61%)	49 (15.81%)	1.38 (0.59-3.23)	0.458
Clinical manifestations				
Health check-ups	418 (63.91%)	11 (28.95%)	ref	
AUB before menopause	170 (25.99%)	13 (34.21%)	2.91 (1.28-6.61)	0.011*
Postmenopausal bleeding	66 (10.09%)	14 (36.84%)	8.06 (3.51-18.51)	<0.001*
Gravidity				
≤1	163 (24.92%)	10 (26.32%)	ref	
2-3	418 (63.91%)	25 (65.79%)	0.98 (0.46-2.08)	0.947
≥4	73 (11.16%)	3 (7.89%)	0.67 (0.18-2.51)	0.552
Endometrial thickness, mean ± SD, mm	9.75±4.98	12.09±4.79	1.07 (1.02-1.13)	0.006*
Endometrial thickness, mm				
<7 mm	168 (25.69%)	2 (5.26%)	ref	
≥7 mm	486 (48.17%)	36 (94.74%)	6.22 (1.48-26.12)	0.013*

NOTE: *P* value is derived from the univariable association analyses between each of the clinical variables and pathological diagnosis. Abbreviations: AUB, abnormal uterine bleeding; SD, standard deviation. **P* value <0.05.

Table 3. Multivariate logistic regression for risk factors of atypical EH+

Characteristics	OR (95% CI)	*P*-value
Age ≥50 y	3.97 (1.17-13.43)	0.027*
Menopause	2.72 (0.59-12.51)	0.198
Comorbidity	2.72 (0.47-2.90)	0.744
AUB before menopause	2.82 (0.97-8.17)	0.057
Postmenopausal bleeding	8.98 (3.26-24.76)	<0.001*
Endometrial thickness ≥7 mm	8.08 (1.86-35.08)	0.005*

Abbreviations: AUB, abnormal uterine bleeding. **P* value <0.05.

postmenopausal bleeding and endometrial thickness ≥7 mm) were analyzed by multiple logistic regression. Age ≥50 years old (OR: 3.97, 95% CI: 1.17-13.43, P=0.027), endometrial thickness ≥7 mm (OR: 8.08, 95% CI: 1.86-35.08, P=0.005) and postmenopausal bleeding (OR: 8.98, 95% CI: 3.26-24.76, P<0.001) were statistically significant (**Table 3**). The Hosmer-Lemeshow goodness-of-fit test yielded a nonsignificant statistic (P=0.234). The nomogram was developed in the primary cohort, with age ≥50 years old, AUB before menopause, postmenopausal bleeding and endometrial thickness ≥7 mm incorporated (**Figure 2**). The prediction model showed good discrimination with area under curve (AUC) of 77.09% (**Figure 3A**). To achieve recall of 100% (38/38) of atypical EH+, we set the cutoff probability at 0.0087597, and the precision was 6.52% (38/583) in the primary cohort. In the independent validation cohort, recall was 100% (13/13) and precision was 6.22% (13/209) (**Figure 4**). The AUC in the validation cohort was 75.81% (**Figure 3B**). For all endometrial lesions, recall was 91.29% (283/310) and

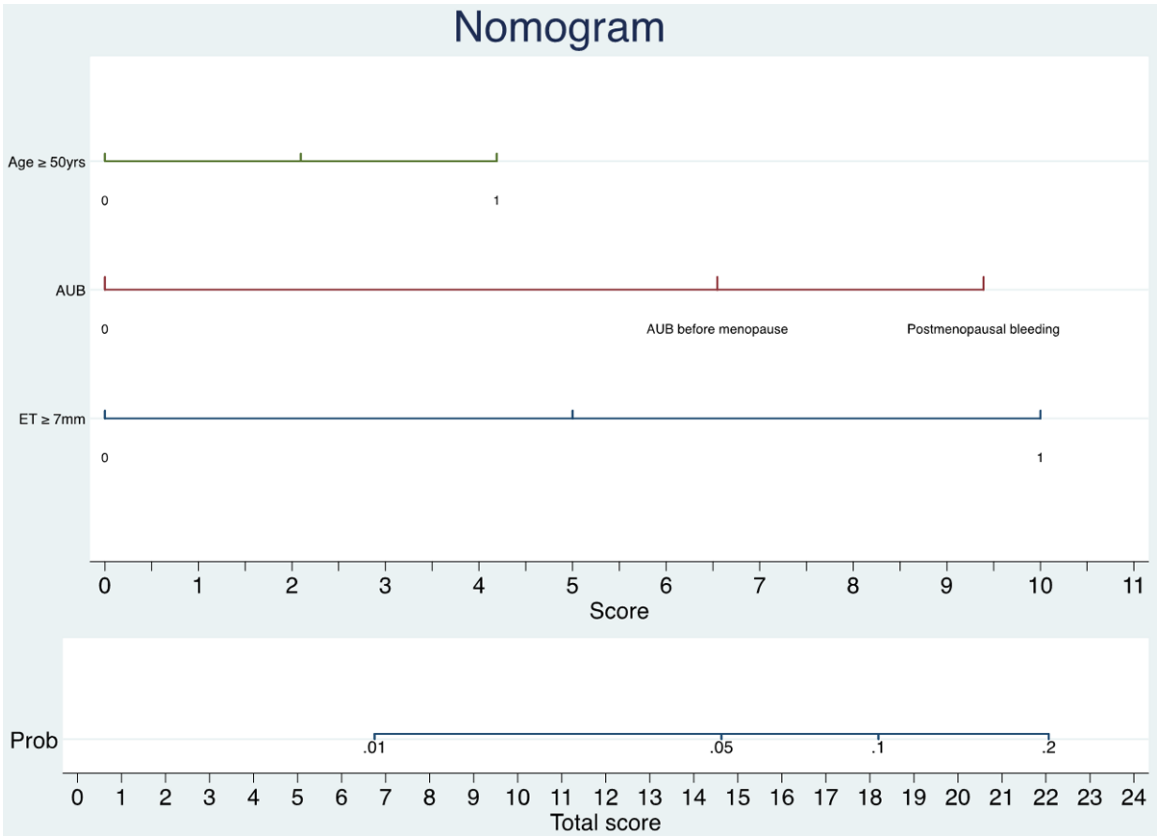

Figure 2. The developed nomogram. The nomogram was developed in the primary cohort, with age ≥50 years old, AUB before menopause, postmenopausal bleeding and endometrial thickness ≥7 mm incorporated. Abbreviations: AUB, abnormal uterine bleeding; ET, endometrial thickness; Prob, probability.

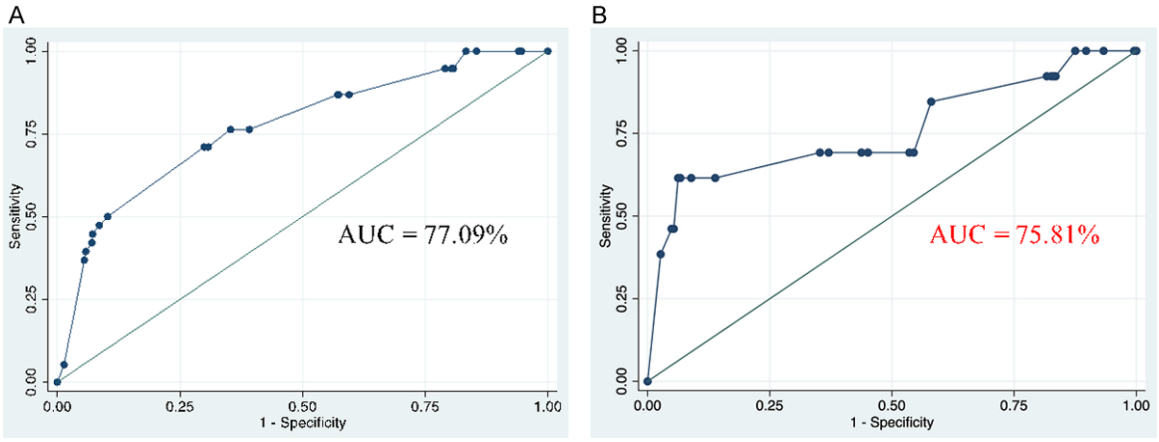

Figure 3. The receiver operator characteristic (ROC) curve of multivariate logistic regression of the risk factors of endometrial lesions for non-uniform endometrial echogenicity.

precision was 48.54% (283/583) in the primary cohort. In the independent validation cohort, recall was 90.91% (100/110) and precision was 47.85% (100/209).

Discussion

TVS has been used extensively as an imaging modality for assessment of endometrial

Primary Cohort	Premalignant+	Premalignant-	Total
Model Positive	38	545	583
Model Negative	0	109	109
Total	38	654	692

Precision = 38/583 = 6.52%

Recall = 38/38 = 100%

Validation Cohort	Premalignant+	Premalignnat-	Total
Model Positive	13	196	209
Model Negative	0	28	28
Total	13	224	237

Precision = 13/209 = 6.22%

Recall = 13/13 = 100%

Figure 4. The precision and recall in primary and validation cohort when the cutoff probability 0.0087597 is set in the multivariable logistic model. Premalignant means atypical EH+.

lesions, but it has demonstrated variable accuracy due to the growth pattern of endometrial lesions. TVS revealed a thickened endometrium or a heterogeneous solid mass in the uterine cavity in the majority of endometrial carcinoma patient [28]. However, the clinical meaning of non-uniform endometrial echogenicity without intracavitary lesions is uncertain. We first showed that nearly half (44.80%) of patients with non-uniform endometrial echogenicity without intracavitary lesions were diagnosed with endometrial lesions, which demonstrated that non-uniform endometrial echogenicity itself was a high-risk factor of endometrial lesions. Endometrial hyperplasia with atypia may develop into cancer in up to 30% of cases [29-31]. The WHO system distinguishes "EH without atypia" (benign) from "atypical EH" (premalignant) based on the presence of cytologic atypia [32]. We demonstrated the proportion of atypical EH+ (premalignant+) was higher than 5%, which exceeded the range of small probability events. Besides, 6.07% of women diagnosed with hyperplasia without atypia were in risk of developing endometrial precancer and carcinoma without intervention. These data strongly indicated the clinical meaning of non-uniform endometrial echogenicity in diagnosis of atypical EH+, especially with the high-risk factors of age ≥50 years old, endometrial thickness ≥7 mm and postmenopausal bleeding .

Since uniform endometrium is regarded normal clinically, there were few studies about the histopathology of uniform endometrium. Hulka CA et al. reviewed the pelvic sonograms and 14 postmenopausal women with breast carcinoma who were being treated with tamoxifen. Pathologic correlation was available in the 11 cases in which adequate tissue was obtained. Sonograms of 9 patients showed heterogeneous endometrium, including 8 showing cystic spaces diagnosed with polyps on pathologic examination and 1 showing a solid and heterogeneous endometrium diagnosed with endometrial carcinoma. Sonograms of 2 patients showed homogeneous, hyperechoic endometrium in 1 patient with an inactive endometrium and 1 patient with hyperplasia without demonstrating the degree of hyperplasia. Besides, sagittal sonograms of all 11 patients with biopsy result showed abnormal endometrial thickening measuring more than 7 mm (range, 8-38 mm; mean, 22 mm) [33]. E. Epstein et al. performed a prospective multicenter study of 1714 women with biopsy-confirmed endometrial carcinoma undergoing standardized transvaginal grayscale and TVS, they found that high-risk tumors, compared with low-risk tumors, were more likely to have non-uniform echogenicity (difference of +7%; 95% CI, +1 to +13%) [15]. M. Dueholm et al. proposed a scoring system to predict endometrial carcinoma using different ultrasound image characteristics which including endometrial echogenicity [34]. However, there is no guideline which kind of patients with non-uniform endometrium should undergo hysteroscopy, or endometrial biopsy, or follow-up. In fact, nearly 1/3 (28.95%, 11/38) of atypical EH+ and 2/3 (66.54%, 181/272) of benign lesions were accidently found with non-uniform endometrial echogenicity in health check-ups. And non-uniform endometrial echogenicity with risk factors is meaningful in screening of atypical EH+.

In order to predict the probability of suffering from atypical EH+, we designed a diagnostic algorithm. When TVS showed non-uniform endometrial echogenicity, predicted probability can be calculated according the status of post-

menopausal bleeding, AUB before menopause, ET ≥7 mm, age ≥50 years old, menopause and comorbidity. To recall 100% of atypical EH+, the cutoff value is 0.0087597. All (100%) atypical EH+ and 91% of endometrial lesions will be diagnosed by hysteroscopy. According to this model, hysteroscopy is recommended if predicted probability is no less than 0.0087587. Blind endometrial biopsy and dilatation and curettage (D&C) are acceptable with higher rate of missed diagnosis. Women with predicted probability less than 0.0087597 are suggested follow-up.

This is the first study to investigate the clinical meaning of non-uniform endometrium diagnosed by TVS by retrospectively analyzing histological results of hysteroscopy and clinical characteristics. For women with non-uniform endometrial echogenicity, the risk of atypical EH+ was significantly higher in patients with risk factors of postmenopausal bleeding, ET ≥7 mm and age ≥50 years old. In this retrospective study, only women referred for hysteroscopy were included in our study and selection bias was inevitable. Since blind curettage lacks accuracy and reliability compared with hysteroscopy, almost all women suspected with endometrial lesions in our hospital underwent hysteroscopy with the popularization of hysteroscopy in the past decade. Therefore, the selection bias is supposed very small. We hoped to include body mass index, however, it was not available in medical records. In future, large prospective studies are anticipated to refine the role of non-uniform endometrial echogenicity.

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Disclosure of conflict of interest

None.

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