

Supplementary Materials

Figure S1. The flowchart of patient selection.

Abbreviations: EAH, endometrial atypical hyperplasia; HE4, human epididymis protein 4.

Figure S2. The ROC curves of serum levels of HE4 in different predicting models. (A-B) The value of HE4 in predicting concurrent EC and intermediate-high-risk EC in all 715 preoperative-EAH patients, based on 2024 NCCN guidelines. (C) The value of HE4 in predicting non-candidates of fertility-sparing treatment in 285 young preoperative-EAH patients.

Notes: Low-risk EC was defined as: (a) endometrioid endometrial cancer, stage IA (FIGO2009), grade 1-2, without lymph-vascular space invasion, age < 60 years; (b) endometrioid endometrial cancer, stage IA (FIGO2009), grade 3, without lymph-vascular space invasion, age < 60 years, without myometrial invasion. All other EC cases except for low-risk EC were defined as intermediate-high-risk EC, based on the NCCN guidelines (version 3.2024).

Abbreviations: HE4, human epididymis protein 4; EAH, endometrial atypical hyperplasia; EC, endometrial cancer; final-EC, endometrial cancer diagnosed by final histopathology; AUC, area under the curve; ROC, receiver operator characteristic.

Figure S3. Univariate and multivariate analyses of factors predicting final-EC for 715 preoperative-EAH patients with and without endometrial thickness by ultrasound.

Notes: Missing data included 41 cases for BMI, 12 for diabetes, 59 for hypertension, 22 for FBG, 10 for CA125, and 92 for endometrial thickness by ultrasound. The categorical variable of serum HE4 levels had a cut-off as 43.5 pmol/L. In multivariate logistic analysis with available endometrial thickness by ultrasound, OR adjusted for age, BMI, menopausal status, diabetes, hypertension, HE4 value, CA125 value, and endometrial thickness by ultrasound. In multivariate logistic analysis without available endometrial thickness by ultrasound, OR adjusted for age, BMI, menopausal status, diabetes, hypertension, HE4 value, and CA125 value. Significant *P* value < 0.05.

Abbreviations: EAH, endometrial atypical hyperplasia; EC, endometrial cancer; BMI, body mass index; FBG, fasting blood glucose; HE4, human epididymis protein 4; CA125, cancer antigen 125; D&C, dilatation and curettage; HSC, hysteroscopy; OR, odds ratio; CI, confidence interval.

Figure S4. Univariate and multivariate analyses of factors predicting concurrent intermediate-high-risk EC for 715 preoperative-EAH patients incorporating hypertension.

Notes: Missing data included 41 cases for BMI, 12 for diabetes, 59 for hypertension, 22 for FBG, 10 for CA125, and 92 for endometrial thickness by ultrasound. The categorical variable of serum HE4 levels had a cut-off as 53.15 pmol/L. In multivariate logistic analysis, OR adjusted for age, menopausal status, hypertension, HE4 value, and CA125 value. Significant *P* value < 0.05. Low-risk EC was defined as: (a) endometrioid endometrial cancer, stage IA (FIGO2009), grade 1-2, without lymph-vascular space invasion, age < 60 years; (b) endometrioid endometrial cancer, stage IA (FIGO2009), grade 3, without lymph-vascular space invasion, age < 60 years, without myometrial invasion. All other EC cases except for low-risk EC were defined as intermediate-high-risk EC, based on the NCCN guidelines (version 3.2024).

Abbreviations: EAH, endometrial atypical hyperplasia; EC, endometrial cancer; BMI, body mass index; FBG, fasting blood glucose; HE4, human epididymis protein 4; CA125, cancer antigen 125; OR, odds ratio; CI, confidence interval; D&C, dilatation and curettage; HSC, hysteroscopy.

Patients diagnosed with EAH preoperatively
from January 2016 to December 2022 (n =1237)

Excluded patients (n = 522) :
received fertility-sparing therapies in six months
before hysterectomy,
complicated other malignant tumors,
underwent hysterectomy $\geq$ three months after
initial diagnosis,
without available data of the levels of serum HE4
within one month before hysterectomy

Study subjects (n = 715)

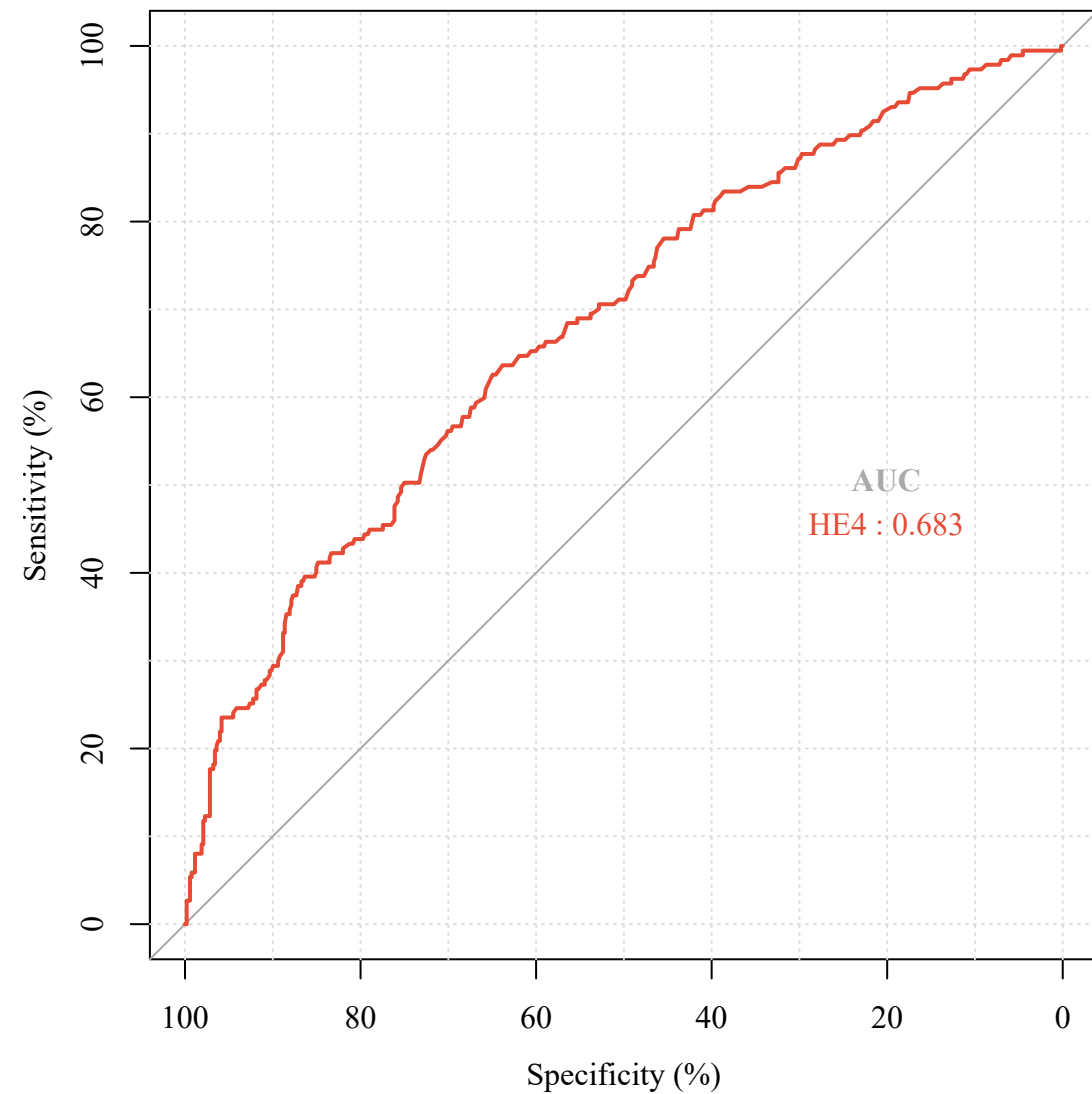
HE4 correlated with
clinicopathological factors

HE4 predicting
intermediate-high-risk EC

HE4 predicting non-candidates of
fertility-preserving therapy in young
patients with age $\leq$ 45 years and
premenopausal status

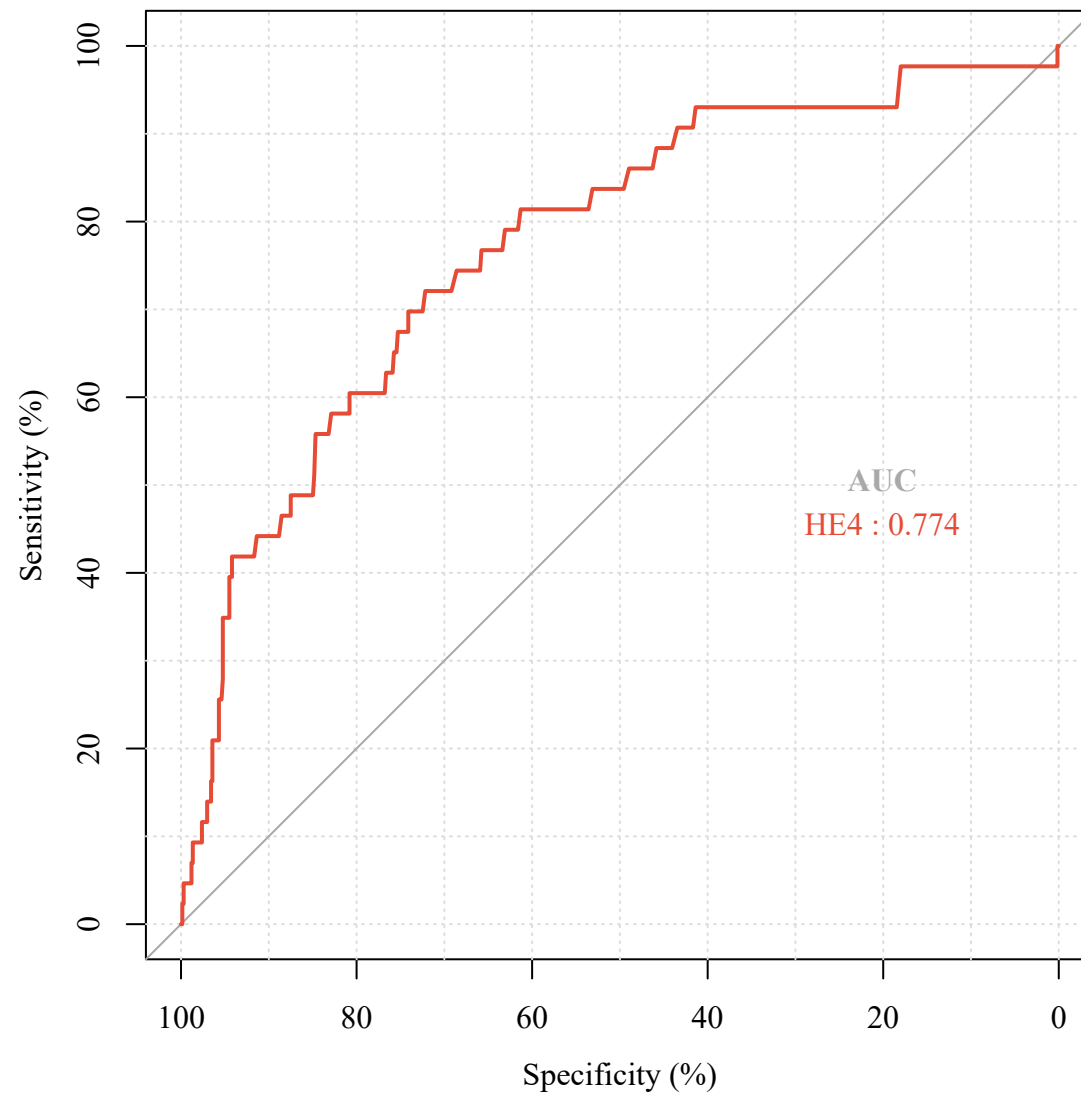
A.

Concurrent EC



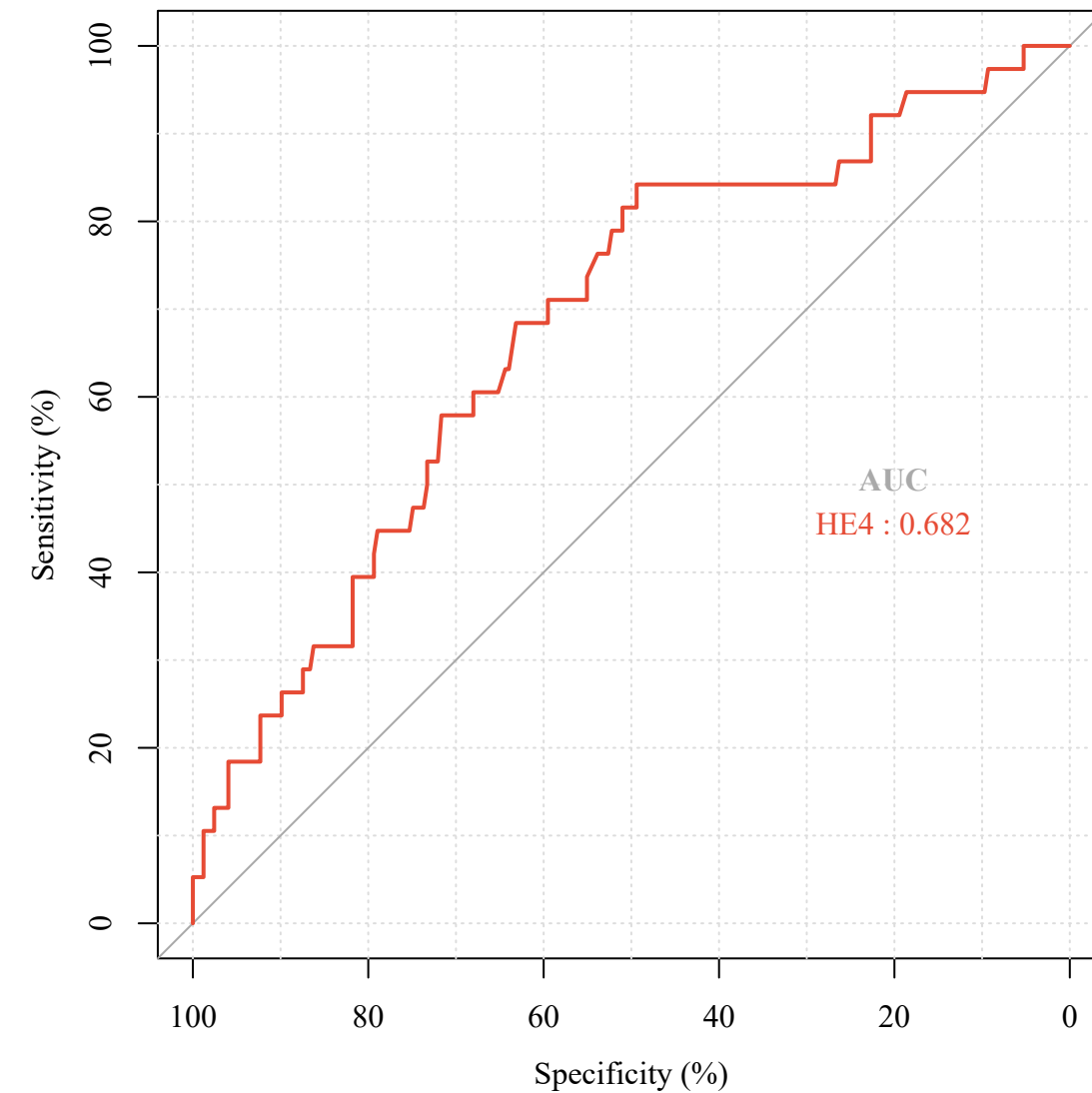
B.

Concurrent intermediate-high-risk EC

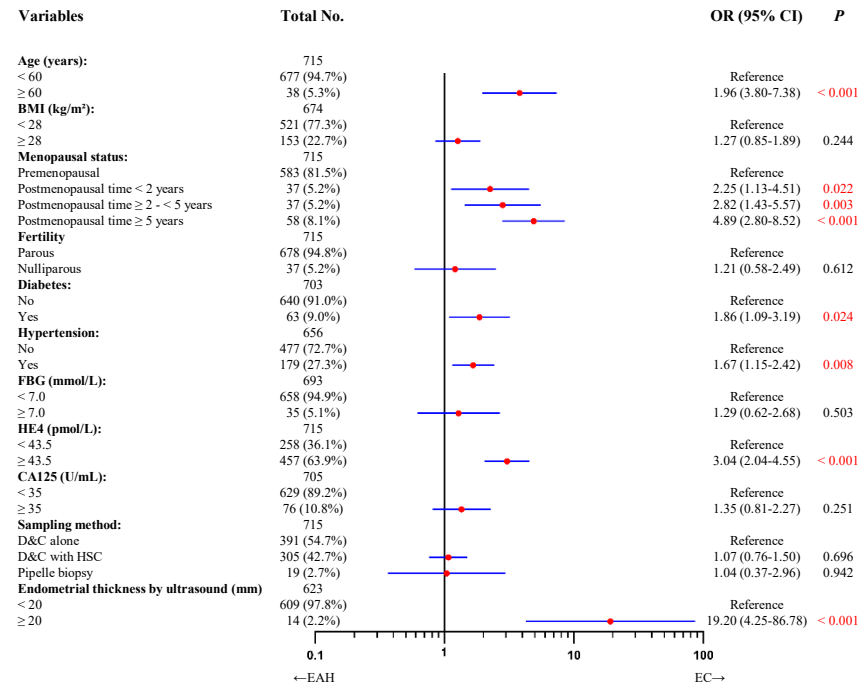


C.

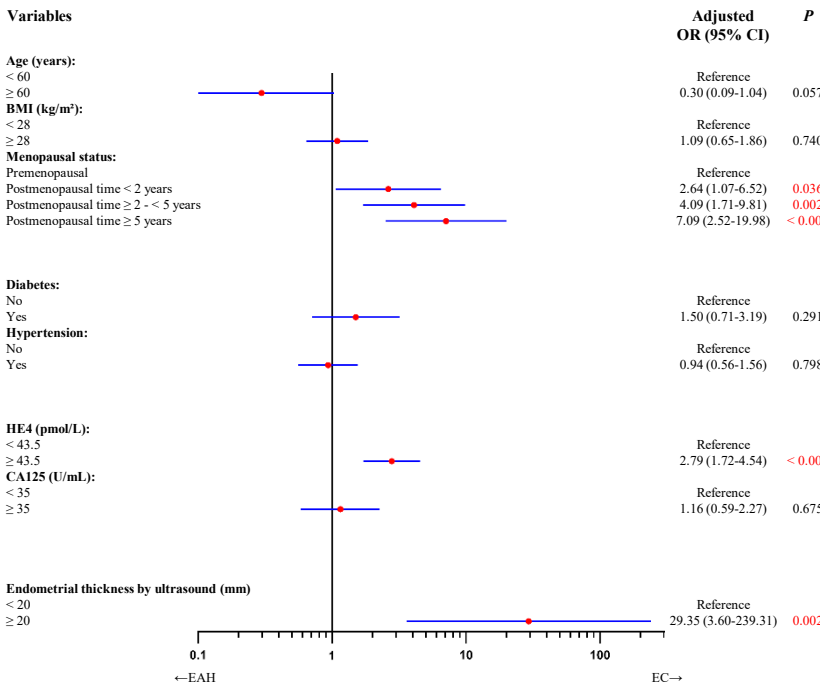
Non-candidates for fertility-sparing treatment



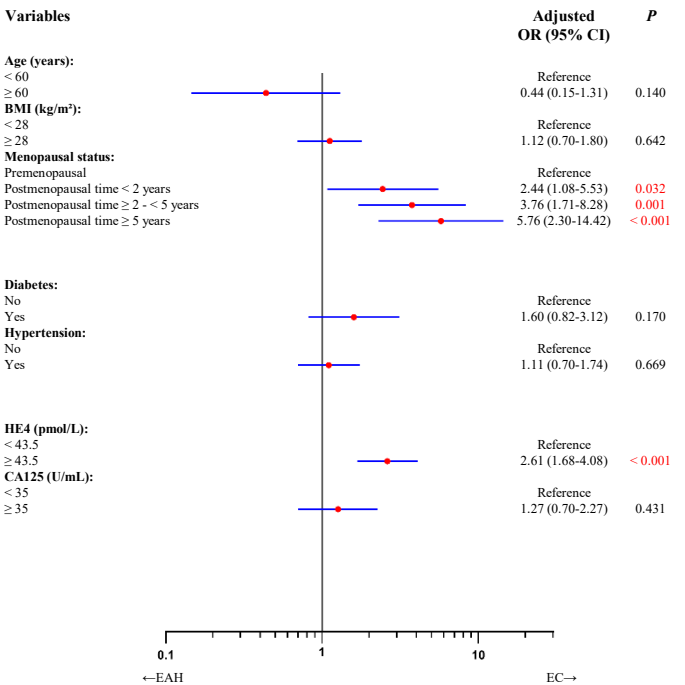
Univariate Analysis



Multivariate Analysis with Available Endometrial Thickness



Multivariate Analysis without Available Endometrial Thickness



Univariate Analysis

Multivariate Analysis

