

Serum CA125 and HE4 as Diagnostic Biomarkers in Endometrial Cancer- Supplementary Materials

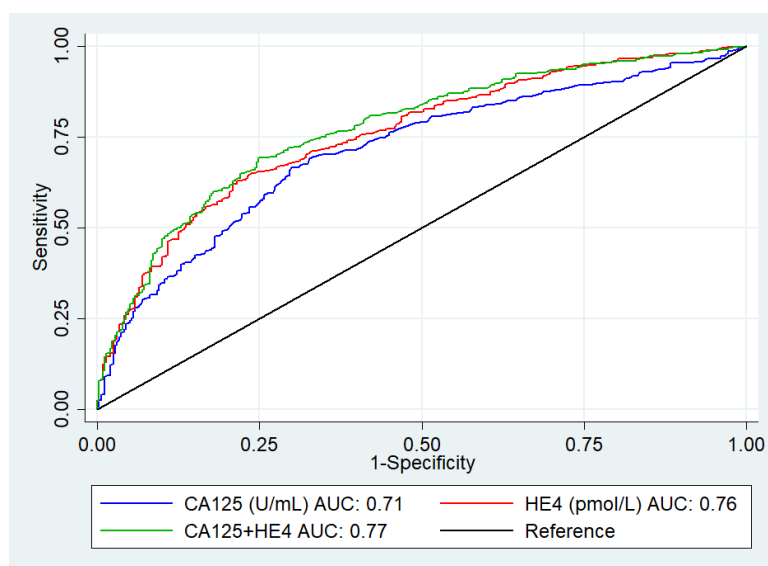


Figure S1. ROC analysis of serum CA125 and serum HE4 for the detection of endometrial cancer. $n=755$. CA125 AUC 0.71 (95%CI 0.68-0.75). HE4 AUC 0.76 (95%CI 0.72-0.79). Combined AUC 0.77 (95%CI 0.74-0.81).

Table S1. Diagnostic accuracy of CA125 and HE4 for the detection of endometrial cancer at **optimal** thresholds.

	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV (95%CI)	NPV (95%CI)
a. Total cohort ($n=755$, EC 397 (53%))				
CA125 (≥ 15 U/mL)	66.8 (61.9-71.4)	69 (63.9-73.8)	70.5 (65.6-75.0)	65.2 (60.1-70.0)
HE4 (≥ 99 pmol/L)	65.2 (60.3-69.9)	75.7 (70.9-80.1)	74.9 (69.9-79.3)	66.3 (61.4-70.8)
Combined (either positive)	82.6 (78.5-86.2)	57.3 (52.0-62.4)	68.2 (63.8- 72.3)	74.8 (69.2-79.8)
b. Pre-menopausal ($n=108$ EC=58 (54%))				
CA125 (≥ 15 U/mL)	62.1 (48.4-74.5)	70 (55.4-82.1)	70.6 (56.2-82.5)	61.4 (47.6-74)
HE4 (≥ 99 pmol/L)	34.5 (22.5-48.1)	94 (83.5-98.7)	87 (66.4-97.2)	55.3 (44.1-66.1)
Combined (either positive)	70.7 (57.3-81.9)	66 (51.2-78.8)	70.7 (57.3-81.9)	66 (51.2-78.8)
c. Postmenopausal ($n= 643$ EC= 338 (53%))				
CA125 (≥ 15 U/mL)	67.5 (62.2-72.4)	69.2 (63.7-74.3)	70.8 (65.5-75.7)	65.7 (60.3-70.9)
HE4 (≥ 99 pmol/L)	70.7 (65.5-75.5)	72.8 (67.4-77.7)	74.2 (69.1-78.9)	69.2 (63.8-74.2)

Combined (either positive)	84.6 (80.3-88.3)	56.1 (50.3-61.7)	68.1 (63.4-72.5)	76.7 (70.6-82.1)
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CI- confidence interval. PPV- positive predictive value. NPV- negative predictive value. n-number. EC- endometrial cancer.

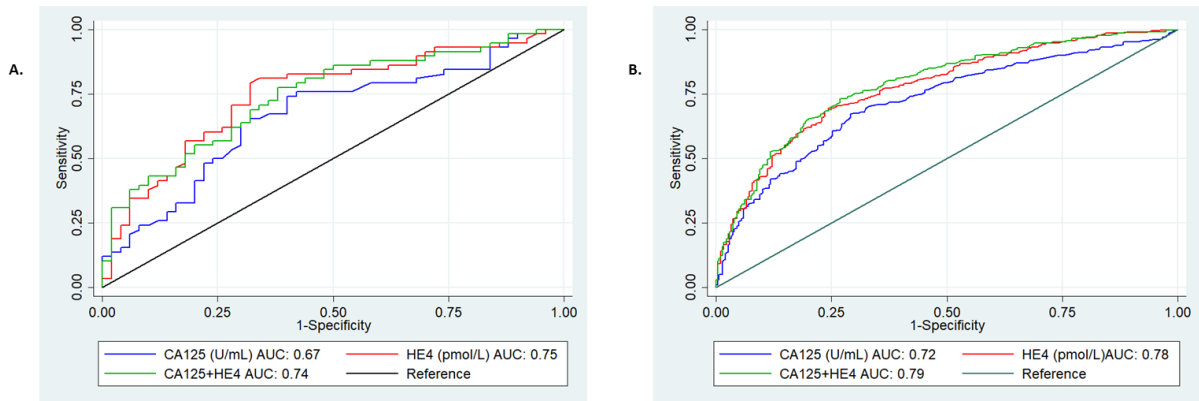


Figure S2. ROC analysis of CA125 and HE4 for the detection of endometrial cancer stratified by menopausal status. **A- Pre menopausal.** CA125 AUC 0.67 (95%CI 0.56-0.77), HE4 AUC 0.75 (0.65-0.84), Combined AUC 0.74 (95%CI 0.65-0.84). **B- Postmenopausal.** CA125 AUC 0.72 (95%CI 0.68-0.76), HE4 AUC 0.78 (95%CI 0.74-0.81), Combined AUC 0.79 (95%CI 0.75-0.82).

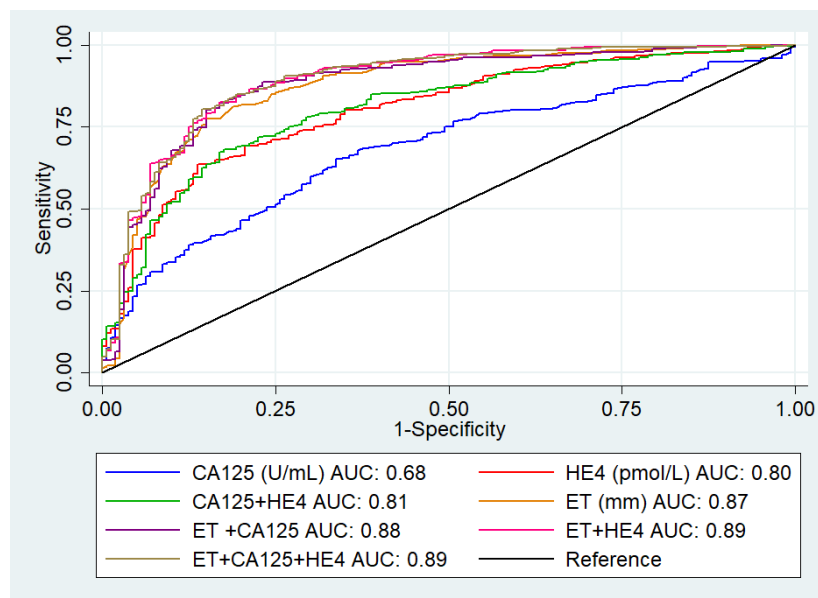


Figure S3. ROC curve analysis of serum markers and endometrial thickness models for the detection of endometrial cancer. CA125 AUC 0.68 (95%CI 0.64-0.73). HE4 AUC 0.80 (95%CI 0.76-0.84). CA125 + HE4 AUC 0.81 (95%CI 0.77-0.85). ET AUC 0.87 (95%CI 0.84-0.91). ET+CA125 AUC 0.88 (0.84-0.91). ET+HE4 AUC 0.89 (95% 0.86-0.92). ET+HE4+CA125 AUC 0.89 (95%CI 0.86-0.92).

Table S2. Univariable and multivariable logistic regression models of serum markers and ET for the prediction of endometrial cancer (n=426, EC= 326 (77%)).

Model	Predictor	Univariable		Multivariable				
		Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value	AUC	Sens	Spec
A. Base model								
ET	Disease status	1.21 (1.16-1.26)	<0.001	1.20 (1.15-1.25)	<0.001	0.88	89.9	70.4
B. Base model + HE4								
HE4	Disease status	1.02 (1.01-1.03)	<0.001	1.01 (1.00-1.02)	0.001	0.89	89.0	72.3
ET				1.17 (1.12-1.23)	<0.001			
C. Base model + HE4 + CA125								
CA125	Disease status	1.04 (1.02-1.06)	<0.001	1.01 (0.99-1.03)	0.29	0.89	89.3	72.3
HE4				1.01 (1.00-1.01)	0.002			
ET				1.17 (1.12-1.22)	<0.001			

OR- odds ratio. CI- confidence interval. AUC- area under the curve. Multivariable analysis adjusted for age and BMI. Akaike Information Criterion (AIC) model A-433.50. AIC model B- 417.91. AIC model C- 418.43.

Comparison of models (likelihood ratio test): A vs B p<0.001. B vs C p=0.22.

Table S3. Univariable and multivariable logistic regression models of serum markers for the prediction of high risk features of endometrial cancer.

Model	Predictor	Univariable Analysis		Multivariable Analysis				
		Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value	AUC	Sens	Spec
HE4	Myometrial Invasion	1.002 (1.001-1.003)	<0.001	1.002 (1.000-1.003)	0.001	0.78	43.1%	88.9%

CA125	MI≥50%	1.001 (0.997- 1.004)	0.63	0.997 (0.993- 1.001)	0.29	0.84	47.2	88.2
HE4				1.003 (1.000- 1.005)	0.03			
MRI				19.0 (7.00- 51.37)	<0.001			

OR- odds ratio. CI- confidence interval. AUC- area under the curve. Multivariable analysis adjusted for histological subtype and grade. AIC model A-176.46. AIC model B- 174.21. AIC model C- 175.09. Comparison of models (likelihood ratio test): A vs B p=0.04. B vs C p=0.29.