Preoperative CA125 and metabolic factors associated with high-risk pathology in endometrial cancer

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Abstract. Molecular classification is now central to endometrial cancer risk assessment, but its implementation in routine practice varies across clinical settings. Against this background, the present retrospective study examined whether routinely available preoperative CA125 and metabolic factors are associated with postoperative high-risk pathological features in endometrial cancer. A total of 188 patients with surgically treated, pathologically confirmed endometrial cancer at Cangzhou Central Hospital Affiliated to Hebei Medical University (Cangzhou, China) between January 2024 and January 2026 were included. Clinical characteristics, metabolic indicators, preoperative CA125, postoperative pathological variables and available molecular classification data were collected. The primary outcome was the presence of any high-risk pathological factor, defined as high-grade/aggressive histology, deep myometrial invasion, lymphovascular space invasion (LVSI), cervical stromal involvement or lymph node metastasis. Overall, 98 patients (52.1%) had at least one high-risk pathological factor. Molecular classification was missing or undetermined in 66 patients (35.1%); these results were therefore treated as contextual exploratory information. In the prespecified multivariable model, age [odds ratio (OR)=1.061; 95% CI, 1.019-1.108; P=0.005] and log(CA125) (OR=2.059; 95% CI, 1.375-3.242; P<0.001) were associated with the composite high-risk pathological phenotype. Exploratory analyses of individual endpoints showed the most consistent CA125 associations with LVSI positivity and lymph node metastasis. BMI, diabetes, hypertension, metabolic syndrome and routine lipid indicators did not show reproducible associations with high-risk pathological status. Overall, higher preoperative CA125 was independently associated with the composite adverse pathological phenotype and may provide complementary preoperative risk information pending prospective validation.

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Abbreviations: FDR, false discovery rate; FIGO, International Federation of Gynecology and Obstetrics; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NGS, next-generation sequencing; NSMP, no specific molecular profile; OR, odds ratio

Key words: endometrial cancer, CA125, metabolic factors, molecular classification, high-risk pathology

Introduction

Endometrial cancer is one of the most common malignancies of the female reproductive tract, with 434,620 new cases of corpus uteri cancer estimated worldwide in 2024 according to GLOBOCAN 2024 (1). The clinical spectrum of endometrial cancer is also changing as population aging, obesity, metabolic abnormalities and shifting reproductive patterns reshape age distribution, comorbidity burden and reproductive history of patients. For clinicians, the challenge is not only the rising disease burden, but also the early recognition of tumors with aggressive pathological behavior.

Risk assessment has traditionally relied on histological type, tumor grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), cervical stromal involvement, lymph node status and International Federation of Gynecology and Obstetrics (FIGO) stage. Bokhman's dualistic model provided an important historical framework, but it cannot fully explain contemporary pathological heterogeneity (2). The 2023 FIGO staging system further incorporated histopathological and molecular information, reflecting the shift from anatomical staging toward integrated risk assessment (3). Nevertheless, high-risk pathological factors such as LVSI and lymph node metastasis are often confirmed only after surgery, and patients within the same stage or histological category may still differ substantially. Conventional pathological factors therefore remain indispensable, but they may be insufficiently precise when used alone.

The Cancer Genome Atlas (TCGA)-based molecular classification, together with its clinical translation through the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), has changed the way endometrial cancer risk is interpreted (4-8). Subtyping based on POLE mutation (POLEmut) status, mismatch repair deficiency, p53 abnormality and no specific molecular profile refines prognostic assessment and, in selected settings, informs adjuvant-treatment discussions (4-10). Routine implementation is less

straightforward. It requires validated immunohistochemistry and sequencing workflows, adequate tumor tissue, specialist interpretation, additional cost and reporting time. In primary hospitals or resource-constrained settings, molecular results may be unavailable, delayed or incomplete when perioperative assessment is needed. This gap does not lessen the value of molecular classification. It instead reflects a common clinical sequence: Risk assessment often starts before complete molecular and postoperative pathological information is available. During this interval, clinicians rely on conventional clinicopathological factors and routinely measured preoperative variables. Even established pathological factors such as LVSI may carry different implications across molecular subgroups (11). Accessible clinical indicators therefore still merit evaluation in the molecular-classification era.

CA125 is one of the serum biomarkers most often used during perioperative assessment of endometrial cancer. Previous studies have associated elevated preoperative CA125 with deep myometrial invasion, extrauterine disease, LVSI and lymph node metastasis (12-14). More recent work has examined CA125 alongside human epididymis protein 4, clinicopathological variables and molecular classification in association to nodal involvement, extrauterine disease and other high-risk pathological features (15-21). Together, these findings support further evaluation of CA125 as a readily available marker of adverse pathological risk.

Metabolic factors are also available in routine care, yet their association with aggressive pathological behavior remains uncertain. Obesity, insulin resistance, chronic inflammation, sex-hormone metabolism and tumor microenvironment alterations are biologically associated to endometrial carcinogenesis (22,23). The clinicopathological evidence is less uniform. Higher BMI has been associated with endometrioid histology, lower-grade tumors, progesterone receptor positivity and molecular-subtype differences (24,25); studies of metabolic syndrome and its components have also reported heterogeneous findings for nodal involvement, adverse pathology and prognosis (26-28). These inconsistencies justify further evaluation of routinely measured metabolic variables, particularly in real-world cohorts where molecular-classification availability is variable.

The present study evaluated the multivariable-adjusted associations of routinely available preoperative CA125 and metabolic factors with a prespecified composite of postoperative adverse pathological features. The analysis used a real-world cohort with incomplete molecular-classification coverage.

Materials and methods

Study population. The present single-center retrospective cohort study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology principles (29). Patients were screened if they were discharged from the Department of Gynecology III of Cangzhou Central Hospital Affiliated to Hebei Medical University (Cangzhou, China) between January 2024 and January 2026 with a discharge diagnosis of malignant endometrial tumor. Eligibility required diagnosis and treatment at the Department of Gynecology III of Cangzhou Central Hospital Affiliated to Hebei Medical University, together with pathological confirmation of primary endometrial cancer. Clinical data, laboratory indicators and postoperative pathological information were retrospectively collected from the electronic medical record system. The data were accessed and analyzed between February and April 2026 for the present study. The inclusion criteria were as follows: i) Pathologically confirmed primary endometrial cancer; ii) available clinical, metabolic and pathological data for analysis; and iii) assessable primary pathological outcome information. Patients were excluded for palliative or conservative treatment, readmission for postoperative complications or metastatic tumors from other primary cancers. Further exclusions were substantial incompleteness of metabolic indicators required for the planned analyses and an indeterminate primary pathological outcome.

During the study period, 356 patients met the time-window and diagnostic screening criteria. Before eligibility confirmation, 50 patients were excluded: 21 underwent palliative or conservative treatment, 9 were readmitted because of postoperative complications and 20 had metastatic tumors from other primary cancers. The remaining 306 patients had received diagnosis and treatment at the center and had pathologically confirmed primary endometrial cancer. Of these, 118 were excluded because metabolic indicators required for the planned analyses were substantially incomplete. The final analytic cohort included 188 patients. To assess potential selection bias, age, CA125 and postoperative pathological factors available in both the final analytic cohort and the excluded eligible patients were extracted for comparison. Metabolic variables that determined final analytic-cohort eligibility were not imputed. The patient selection process is shown in Fig. 1.

The present study was reviewed and approved by the Institutional Review Board of Cangzhou Central Hospital Affiliated to Hebei Medical University (approval no. 2026-154-01) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board, and all data used for analysis were de-identified before statistical processing.

Clinical data collection. General clinical characteristics, metabolic indicators, laboratory test results, postoperative pathological data and molecular classification information were obtained from the electronic medical record system. The clinical and laboratory variables included age, menopausal status, height, weight, BMI, history of diabetes, fasting blood glucose, hypertension, lipid profiles and preoperative serum CA125 level. Pathological and molecular variables included final pathological type, histological grade, depth of myometrial invasion, cervical stromal involvement, LVSI, lymph node metastasis, FIGO stage and molecular classification. All metabolic and blood-based indicators used in the present analysis were measured before surgery. If >1 preoperative value was available for a variable, the measurement closest to the surgery date was used, with priority given to results obtained within 2 weeks before surgery. Serum CA125 was measured as part of routine preoperative laboratory assessment in the hospital clinical laboratory, and the value recorded in U/ml was used for analysis.

Surgical treatment, lymph node assessment and pathological evaluation. All patients in the analytic cohort underwent

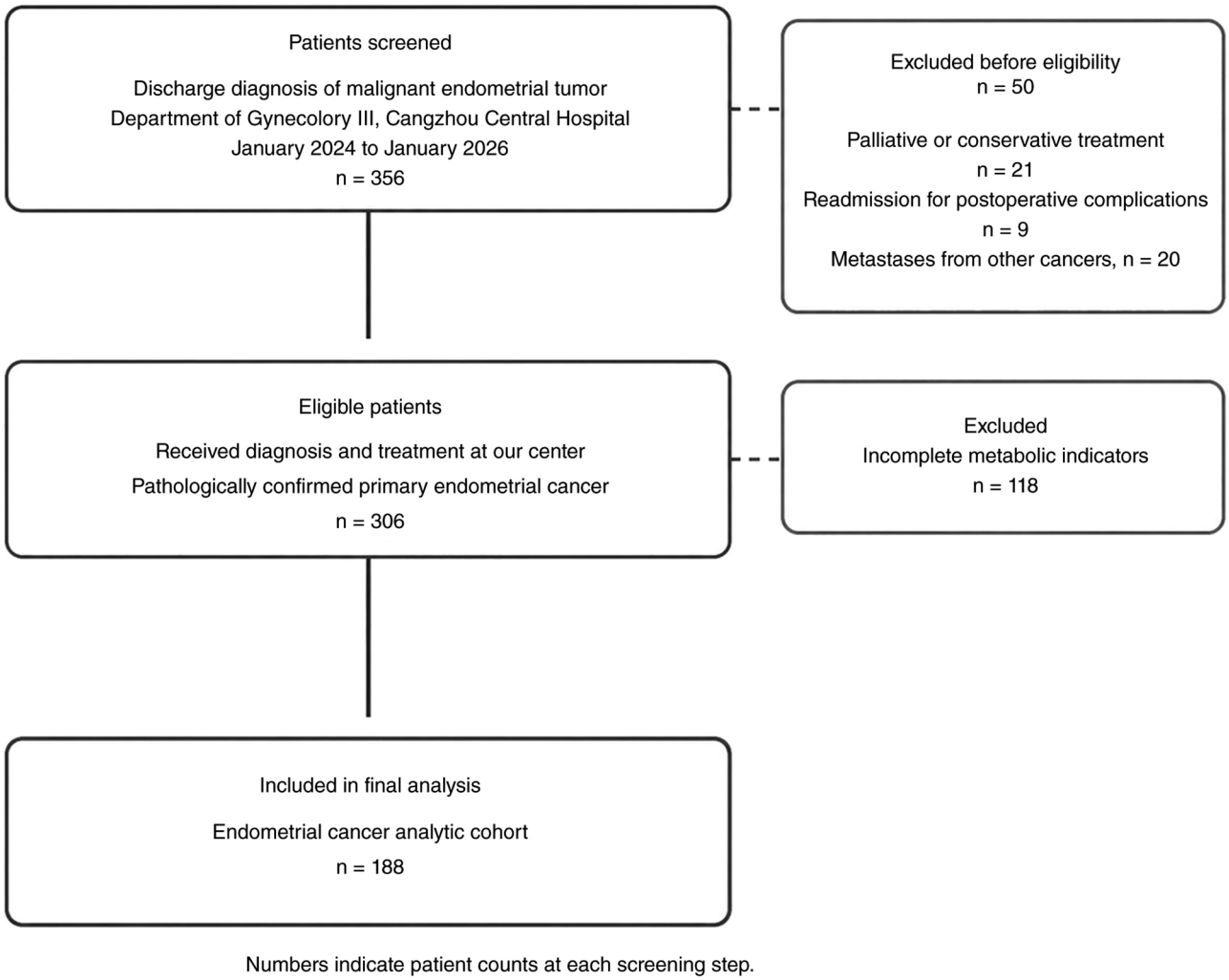

Figure 1. Flow diagram of patient selection.

primary hysterectomy-centered staging surgery with systematic lymphadenectomy. Pelvic lymphadenectomy was performed in every included case. Para-aortic lymphadenectomy was performed according to preoperative evaluation, intraoperative findings, patient-specific clinical considerations and institutional gynecologic oncology practice. Bilateral salpingo-oophorectomy was performed according to age, menopausal status, disease characteristics and clinical judgment. For the present retrospective analysis, lymph node metastasis was defined by pathological identification of metastatic carcinoma in the dissected lymph nodes in the final surgical pathology report.

During the cohort inclusion period (January 2024-January 2026), sentinel lymph-node mapping was not part of the routine institutional pathway because the center did not have a laparoscopic near-infrared fluorescence imaging system for indocyanine green-guided mapping, and the pathology department had not yet established the capability and standardized workflow for sentinel-node ultrastaging. Both the operative imaging pathway and pathological ultrastaging became fully operational in February 2026, after cohort inclusion had ended. Consequently, systematic pelvic lymphadenectomy was the routine institutional approach to nodal assessment during the study period, rather than a procedure selected specifically for the present study. Para-aortic lymphadenectomy remained selective, as aforementioned.

Postoperative pathological evaluation followed standardized institutional procedures and contemporary gynecologic pathology criteria. Histological type, histological grade, depth of myometrial invasion, cervical stromal involvement, LVSI, lymph node status and FIGO stage were abstracted from the final pathology reports. Deep myometrial invasion was defined as tumor invasion involving ≥1/2 of the myometrial thickness. LVSI was defined as the presence of tumor cells within endothelial-lined lymphatic or vascular spaces. Cervical stromal involvement referred to tumor infiltration into the cervical stroma. Pathological assessment had been completed as part of routine clinical diagnosis before construction of the study database and before statistical grouping; therefore, the pathologists were not aware of the subsequent statistical comparisons. Cases with diagnostically challenging findings or key high-risk pathological features were finalized through routine senior review or departmental consensus according to institutional practice. FIGO stage was assigned according to the 2023 FIGO staging system using final surgical pathology and available molecular information. For early-stage disease, POLEmut and p53abn could modify stage when molecular results were available, whereas stages III and IV remained

based on surgical/anatomical findings, with the molecular class recorded when known. Cases with available molecular results were staged using all available information, and cases without complete molecular data were assigned a 2023 FIGO stage without an unavailable molecular modifier.

Histological grading was applied only to endometrioid carcinomas using the FIGO three-tier system. G1, G2 and G3 were defined by ≤5, 6-50 and >50% non-squamous solid growth, respectively. Marked nuclear atypia involving >50% of tumor cells increased the grade by one. Serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma and aggressive mixed carcinoma were not assigned a numerical FIGO grade and were classified as aggressive non-endometrioid histotypes. Mixed tumors containing an aggressive component were classified as aggressive histotypes. Histotype assignments were verified against the final pathology reports before reanalysis.

Molecular classification assessment. For patients who underwent molecular testing, classification was assigned using routine immunohistochemistry (IHC) and next-generation sequencing (NGS) on formalin-fixed, paraffin-embedded tumor tissue. IHC assessed mismatch repair (MMR) protein expression [MutL homolog 1, postmeiotic segregation increased 2, MutS homolog (MSH) 2 and MSH6] and p53 expression; NGS was used to detect pathogenic or likely pathogenic POLE exonuclease-domain mutations. Loss of nuclear expression of any MMR protein in tumor cells, with retained internal control staining, was interpreted as MMR deficiency. p53 abnormality (p53abn) was assigned when the IHC pattern showed aberrant overexpression, complete absence/null pattern or cytoplasmic expression. Tumors without POLEmut, MMRd or p53abn features were classified as no specific molecular profile (NSMP). When >1 molecular feature was present, classification followed the routine hierarchical interpretation used for TCGA-surrogate endometrial cancer molecular typing. Cases without complete molecular results because of small tumor foci, insufficient tumor tissue, technically undetermined results or patient refusal were recorded as missing/undetermined molecular classification. In routine care, molecular testing was undertaken after clinician-patient discussion and patient agreement.

Variable definitions and grouping. Given the limited sample size, BMI was further dichotomized into a normal-weight group (BMI <25 kg/m^2) and an overweight/obese group (BMI ≥25 kg/m^2) to analyze the association between body weight status and high-risk pathological features.

Metabolic syndrome was defined according to the 2004 Chinese Diabetes Society (CDS) criteria (30), with modifications based on data availability. Patients were classified as having metabolic syndrome if they met ≥3 of the following four criteria: i) BMI ≥25 kg/m^2; ii) a documented history of diabetes or fasting blood glucose ≥6.1 mmol/l; iii) a documented history of hypertension or current antihypertensive treatment; and iv) triglycerides ≥1.7 mmol/l or high-density lipoprotein cholesterol <1.0 mmol/l. The original CDS criteria also include 2-h post-load plasma glucose ≥7.8 mmol/l as a hyperglycemia criterion and measured blood pressure ≥140/90 mmHg as a hypertension criterion; these variables were unavailable in the retrospective dataset and were therefore not included. As all patients were women, the female high-density lipoprotein cholesterol threshold was applied.

The following five pathological features were defined as high-risk pathological factors: High-grade/aggressive histology, deep myometrial invasion (myometrial invasion depth ≥1/2), LVSI positivity, cervical stromal involvement and lymph node metastasis. The histology component comprised grade G3 endometrioid carcinoma and aggressive non-endometrioid histotypes, including serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma and aggressive mixed carcinoma.

The primary outcome variable was the presence of any high-risk pathological factor. Patients with ≥1 of the aforementioned features were classified as positive; those without any of these features were classified as negative. This composite outcome served as a pragmatic indicator of whether a patient had ≥1 adverse postoperative pathological feature. Its components were not assumed to share identical biological mechanisms or equivalent prognostic weight. The composite outcome was therefore interpreted as a descriptive high-risk pathological phenotype. High-grade/aggressive histology, deep myometrial invasion, LVSI positivity, cervical stromal involvement and lymph node metastasis were also analyzed separately as exploratory individual outcomes to examine heterogeneity within this phenotype.

Statistical analysis. Continuous variables are presented as median (interquartile range), and categorical variables as counts and percentages. Between-group comparisons used the Wilcoxon rank-sum test or Fisher's exact test, as appropriate. As CA125 had a skewed distribution, it was natural log-transformed before regression analyses.

Multivariable logistic regression was used to evaluate factors associated with the presence of any high-risk pathological factor. The main model included five prespecified clinical variables: Age, BMI, diabetes, hypertension and log(CA125). These variables were selected according to clinical availability, data completeness, outcome event number and avoidance of overlapping metabolic definitions. Metabolic syndrome was not entered together with its component variables. The extended sensitivity model additionally considered menopausal status and molecular-classification availability. Histological type was not included as an additional covariate because aggressive non-endometrioid histology was included in the definition of the composite outcome. Complete-case sensitivity models restricted to patients with available molecular classification data are presented in Table SI, and analyses of potential selection bias arising from incomplete metabolic indicators are presented in Tables SII and SIII

Exploratory analyses of individual high-risk pathological factors used univariable logistic regression. Differences in BMI and CA125 across molecular subtypes were assessed using the Kruskal-Wallis test or Fisher's exact test. Exploratory multiple testing was adjusted using the Benjamini-Hochberg false discovery rate (FDR) method. Missing clinical or molecular data were not imputed. Results are reported as odds ratios (ORs) with 95% CIs. All analyses were performed using R (version 4.6.0; Posit Software, PBC). A two-sided $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Baseline clinicopathological characteristics of the study cohort.

Characteristic	Overall, n=188
Age, years	58 (54-63)
Age group	
<55 years	50 (26.6%)
≥55 years	138 (73.4%)
Menopausal status	
Premenopausal	65 (34.6%)
Postmenopausal	123 (65.4%)
BMI, kg/m^2	26.95 (24.17-29.84)
BMI group, kg/m^2	
<25	59 (31.4%)
≥25	129 (68.6%)
Diabetes	
No	152 (80.9%)
Yes	36 (19.1%)
Hypertension	
No	88 (46.8%)
Yes	100 (53.2%)
Metabolic syndrome	
No	127 (67.6%)
Yes	61 (32.4%)
Lipid profile, mmol/l	
Triglycerides	1.37 (0.97-1.90)
Total cholesterol	4.84 (4.11-5.48)
High-density lipoprotein cholesterol	1.25 (1.07-1.43)
Low-density lipoprotein cholesterol	2.81 (2.32-3.34)
CA125, U/ml	18.20 (12.67-32.00)
Histological type	
Endometrioid	157 (83.5%)
Aggressive non-endometrioid	31 (16.5%)
Molecular classification	
POLEmut	9 (4.8%)
Mismatch repair deficiency	36 (19.1%)
No specific molecular profile	52 (27.7%)
p53abn	25 (13.3%)
Missing/undetermined	66 (35.1%)
Histological grade	
Endometrioid grade 1 + grade 2	130 (69.1%)
Endometrioid grade 3	27 (14.4%)
Deep myometrial invasion	
No	143 (76.1%)
Yes	45 (23.9%)
Cervical stromal involvement	
No	166 (88.3%)
Yes	22 (11.7%)
LVSI	
No	139 (73.9%)
Yes	49 (26.1%)
Lymph node metastasis	
No	165 (87.8%)
Yes	23 (12.2%)
FIGO 2023 stage[a]	
Stage I	120 (63.8%)
Stage II	43 (22.9%)
Stage III	21 (11.2%)
Stage IV	4 (2.1%)

[a]FIGO stage was assigned according to the 2023 FIGO staging system. Numerical FIGO grade was applied only to endometrioid carcinomas. Serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma and aggressive mixed carcinoma were classified as aggressive histotypes and recorded as not applicable for numerical grade. FIGO; International Federation of Gynecology and Obstetrics.

Results

Baseline characteristics and distribution of high-risk pathological factors. A total of 188 patients were included. The median age was 58 years, and the median BMI was 26.95 kg/m^2; 129 patients (68.6%) had BMI ≥25 kg/m^2. Overall, 123 patients (65.4%) were postmenopausal, 36 (19.1%) had diabetes, 100 (53.2%) had hypertension and 61 (32.4%) met the criteria for metabolic syndrome. Table I summarizes the main clinical, metabolic, pathological and molecular characteristics.

Based on the composite definition, 98 patients (52.1%) were positive for ≥1 high-risk pathological factor and 90 (47.9%) were negative. The individual factors were distributed as follows: High-grade/aggressive histology in 58 patients (30.9%), deep myometrial invasion in 45 (23.9%), LVSI positivity in 49 (26.1%), cervical stromal involvement in 22 (11.7%) and lymph node metastasis in 23 (12.2%).

Distribution of molecular subtypes. Molecular classification was available for 122 of 188 patients (64.9%). With the total cohort as the denominator, 52 patients (27.7%) were classified as NSMP, 36 (19.1%) as MMRd, 25 (13.3%) as p53abn and 9 (4.8%) as POLEmut. The remaining 66 patients (35.1%) had missing or undetermined molecular classification. The main reasons were small postoperative tumor foci, insufficient available tumor tissue for molecular testing or patient refusal of further molecular testing.

Patients without complete molecular results did not differ notably from those with available molecular classification data in age, BMI, CA125, menopausal status, diabetes, hypertension, metabolic syndrome or pathological type. The proportion positive for any high-risk pathological factor was lower in the missing/undetermined group than in the available group (39.4 vs. 59.0%; P=0.014), and the difference in FIGO stage distribution approached statistical significance (P=0.051). Missing molecular classification should therefore not be assumed to be completely random, as it may bias estimates of the association between molecular subtype distribution and high-risk pathological factors. Detailed comparisons are provided in Table SIV.

Table II. Comparison between patients with and without any high-risk pathological factor.

Variable	Negative group (n=90)	Positive group (n=98)[a]	P-value
Age, years	56.00 (52.25-61.75)	60.00 (57.00-66.00)	<0.001
BMI, kg/m^2	27.12 (25.25-30.47)	26.84 (23.14-29.42)	0.127
BMI group			0.028
<25 kg/m^2	21 (23.3%)	38 (38.8%)	
≥25 kg/m^2	69 (76.7%)	60 (61.2%)	
Postmenopausal	49 (54.4%)	74 (75.5%)	0.003
Diabetes	15 (16.7%)	21 (21.4%)	0.461
Hypertension	47 (52.2%)	53 (54.1%)	0.884
Metabolic syndrome	32 (35.6%)	29 (29.6%)	0.437
Triglycerides, mmol/l	1.39 (0.91-2.19)	1.31 (1.01-1.77)	0.806
Total cholesterol, mmol/l	4.75 (4.09-5.29)	4.97 (4.17-5.68)	0.115
High-density lipoprotein cholesterol, mmol/l	1.27 (1.07-1.42)	1.25 (1.06-1.46)	0.829
Low-density lipoprotein cholesterol, mmol/l	2.75 (2.31-3.33)	2.84 (2.34-3.34)	0.412
CA125, U/ml	16.61 (11.53-23.40)	22.52 (13.43-38.48)	0.005
Molecular subtype[b]			0.034
No specific molecular profile	28 (56.0%)	24 (33.3%)	
Mismatch repair deficiency	13 (26.0%)	23 (31.9%)	
p53abn	5 (10.0%)	20 (27.8%)	
POLEmut	4 (8.0%)	5 (6.9%)	

[a]The composite outcome comprised high-grade/aggressive histology, deep myometrial invasion ≥1/2, lymphovascular space invasion positivity, cervical stromal involvement or lymph node metastasis. High-grade/aggressive histology was defined as grade G3 endometrioid carcinoma or an aggressive non-endometrioid histotype. [b]The molecular subtype comparison included only patients with available molecular classification data: 50 in the negative group and 72 in the positive group. POLEmut, POLE mutation; p53abn, p53 abnormality.

Table SV presents the exploratory comparisons of BMI and CA125 across molecular subtypes. At the nominal level, BMI appeared higher in the NSMP group, whereas CA125/log(CA125) appeared relatively higher in the MMRd group. After FDR correction across the exploratory molecular-subtype indicators, all corresponding q-values =0.128. These patterns indicate that molecular background may be relevant when routine clinical indicators are interpreted, although confirmation in cohorts with more complete molecular classification is required.

Comparison between patients with and without any high-risk pathological factor. Patients positive for any high-risk pathological factor were older than negative patients, with median ages of 60 and 56 years, respectively (P<0.001). The positive group also had a higher proportion of postmenopausal patients (75.5 vs. 54.4%; P=0.003) and a higher CA125 level (22.52 vs. 16.61 U/ml; P=0.005). BMI as a continuous variable did not differ significantly between groups; the median values were 27.12 kg/m^2 in the negative group and 26.84 kg/m^2 in the positive group (P=0.127). Diabetes (P=0.461), hypertension (P=0.884), metabolic syndrome (P=0.437), TG (P=0.806), total cholesterol (TC; P=0.115), HDL-C (P=0.829) and low-density lipoprotein cholesterol (LDL-C; P=0.412) showed no statistically significant differences between groups. Among the 122 patients with available molecular classification data, molecular subtype distribution differed between groups (P=0.034), with p53abn being more frequent in the high-risk group (Table II).

Additional exploratory analyses using dichotomized BMI are provided in Table SVI. The proportion of patients with BMI ≥25 kg/m^2 was lower in the group positive for any high-risk pathological factor than in the negative group. This pattern was not consistent across individual high-risk pathological factors and was not retained as a primary finding.

Multivariable logistic regression for any high-risk pathological factor. Multivariable logistic regression used the presence of any high-risk pathological factor as the dependent variable and age, BMI, diabetes, hypertension and log(CA125) as independent variables (Table III). In this prespecified clinical-variable model, increasing age was associated with positivity for any high-risk pathological factor (OR=1.061; 95% CI, 1.019-1.108; P=0.005). Higher log(CA125) showed a similar association (OR=2.059; 95% CI, 1.375-3.242; P<0.001). BMI (P=0.128), diabetes (P=0.914) and hypertension (P=0.461) did not reach statistical significance. The model provides adjusted estimates for routinely available clinical variables.

Sensitivity analyses supported the same qualitative interpretation for log(CA125). In the extended model additionally considering menopausal status and molecular-classification availability, log(CA125) remained associated with positivity for any high-risk pathological factor (OR=2.256; 95% CI, 1.435-3.548; P<0.001), while missing/undetermined molecular classification was also associated with the outcome (OR=0.437;

Table III. Multivariable logistic regression for any high-risk pathological factor.

Variable	Odds ratio	Lower 95% CI	Upper 95% CI	P-value
Age	1.061	1.019	1.108	0.005
BMI	0.939	0.865	1.017	0.128
Diabetes	0.955	0.411	2.220	0.914
Hypertension	0.778	0.396	1.509	0.461
log(CA125)	2.059	1.375	3.242	<0.001

Odds ratios for age, BMI and log(CA125) are reported per one-unit increase; CA125 was natural-log transformed.

95% CI, 0.222-0.860; P=0.017). Among patients with available molecular classification data, log(CA125) remained associated with the outcome in both the complete-case clinical-variable model (OR=2.270; 95% CI, 1.285-4.011; P=0.005) and the model additionally including molecular subtype (OR=2.209; 95% CI, 1.216-4.015; P=0.009). Detailed estimates are reported in Tables SI and SVII.

Exploratory analysis of individual high-risk pathological factors. To examine heterogeneity within the high-risk pathological phenotype, each individual high-risk pathological factor was analyzed as a separate exploratory outcome. Univariable logistic regression models included age, BMI, menopausal status, diabetes, hypertension, metabolic syndrome, lipid indicators and CA125. These analyses were not adjusted for all potential confounders and were interpreted with reference to both FDR correction and consistency of association patterns. After FDR correction, the associations of log(CA125) with LVSI positivity and lymph node metastasis were relatively stable, as were the associations of age and menopausal status with deep myometrial invasion. Log(CA125) also showed directionally concordant associations with deep myometrial invasion and cervical stromal involvement, although the statistical evidence was weaker after correction for multiple comparisons. The present findings are reported primarily as exploratory association signals. Diabetes, hypertension, metabolic syndrome, TG, TC and HDL-C did not show consistent associations with the individual high-risk pathological factors. Detailed estimates are provided in Table SVIII.

Observed selection-bias assessment. As 118 eligible patients were excluded for incomplete metabolic indicators, an observed selection-bias assessment was performed as a supplementary analysis. Age (P=0.991), log(CA125) (P=0.582) and positivity for any high-risk pathological factor (P=0.638) showed no clear imbalance between the final analytic cohort and excluded eligible patients. In the all-eligible model among patients with available CA125 and pathological outcome data, log(CA125) remained associated with positivity for any high-risk pathological factor (OR=1.858; 95% CI: 1.366-2.528; P<0.001). The interaction between log(CA125) and inclusion status was not statistically significant (P=0.807), suggesting that the observed CA125 association was not driven solely by inclusion into the final analytic cohort. Detailed results are provided in Tables SII and SIII and Fig. S1.

Discussion

The present exploratory single-center study evaluated multivariable-adjusted associations between routinely available preoperative indicators and a composite adverse pathological phenotype in 188 patients. The analysis provides setting-specific effect estimates from a real-world cohort with incomplete molecular-classification coverage. Over half of the patients had ≥1 high-risk pathological factor. In the selected-variable multivariable model, age and log(CA125) were associated with the composite high-risk pathological phenotype. Supplementary sensitivity analyses supported the same qualitative interpretation for log(CA125), while also accounting for menopausal status and molecular-classification availability. The component endpoints did not follow identical association patterns. For this reason, the composite endpoint is best regarded as a descriptive phenotype of overall adverse pathological status, rather than as a standardized prognostic risk category.

Previous studies have evaluated preoperative CA125 across several complementary clinical settings. Jiang *et al* (12) and LyBarger *et al* (13) related CA125 thresholds or strata to pathological extent, LVSI, lymph node metastasis and survival in retrospective cohorts. Lombaers *et al* (16) focused on high-grade disease, whereas Crha *et al* (18) and Barr *et al* (19) combined CA125 with HE4 or imaging. Miller *et al* (17) developed models for LVSI and lymph node metastasis, and Reijnen *et al* (14) synthesized biomarker performance for nodal disease in a systematic review and meta-analysis. Neilson *et al* (15) examined CA125 in a fully molecularly classified ProMisE cohort. Cooley *et al* (20) investigated prediagnostic early detection, whereas Han *et al* (21) integrated molecular and clinical variables in a nodal-prediction model. The present study addresses a related but distinct question by modeling CA125 as a continuous log-transformed variable alongside routinely documented metabolic factors. It evaluates a prespecified five-component postoperative high-risk pathological phenotype and its individual components in a real-world cohort with incomplete molecular-classification coverage.

The present findings align with earlier evidence that higher CA125 accompanies more extensive or invasive endometrial cancer (12-16). The associations with LVSI and lymph node metastasis are particularly consistent with the observations of LyBarger *et al* (13) and subsequent endpoint-specific models (17,18,21). By contrast, Barr *et al* (19) found that

CA125 at a fixed cut-off did not improve imaging-based assessment of selected high-risk features. This difference may reflect variation in study populations, biomarker combinations, outcome definitions and the continuous modeling of CA125 in the present analysis. Direct comparisons of predictive performance are not possible because the present study neither derived a clinical threshold nor developed or validated a prediction model. Unlike earlier studies, the present study did not evaluate survival (12,15,16), diagnostic or predictive performance (14,17,18,21) or prediagnostic cancer detection (20). Accordingly, the contribution of the present study is a setting-specific extension rather than a new clinical application of CA125. Continuous log(CA125) remained associated with the composite postoperative high-risk pathological phenotype after adjustment for age, BMI, diabetes and hypertension. Component-specific analyses showed the most consistent signals for LVSI and lymph node metastasis. Routine metabolic indicators showed no reproducible pattern across the composite and individual outcomes, consistent with the heterogeneous metabolic evidence reported elsewhere (22-28,31).

Although CA125 is already used as an adjunct in preoperative assessment, its association with the spectrum of postoperative high-risk pathological features remains incompletely characterized. In the present study, higher log(CA125) was associated with higher odds of having ≥1 postoperative high-risk pathological factor after adjustment for age, BMI, diabetes and hypertension. The most consistent component-specific associations were observed for LVSI and lymph node metastasis. These findings extend the clinical context of CA125 by indicating that it may provide complementary preoperative information on the likelihood of invasive pathological features, particularly in real-world settings with incomplete molecular classification. They also support further evaluation of CA125 as a candidate variable in multivariable preoperative risk models. However, these associations do not justify changing standard guideline-based staging or pathological review on the basis of CA125 alone. Prospective validation is required to determine its incremental predictive value and identify clinically informative thresholds.

The natural-log transformation addressed the right skew and does not represent a distinct biological form of CA125. Within the present observational data, circulating CA125 is best interpreted as a downstream marker of mucin-16 (MUC16) production and shedding, tumor burden or tissue disruption. The data do not establish that circulating CA125 directly causes LVSI, lymph node metastasis or other adverse pathological features. Serum CA125 and cell-associated MUC16 are biologically distinct, so this interpretation does not exclude a functional role for the membrane-associated molecule.

In the absence of inflammatory stimulation, basal MUC16 expression has been detected in endometrial adenocarcinoma cell lines (32). Peritoneal mesothelial cells can also release CA125 constitutively, indicating that circulating CA125 may include a non-tumor contribution (33). Normal endometrial epithelium shows constitutive MUC16 expression (34), and primary cultures of normal and malignant endometrial epithelium release CA125 under basal culture conditions (35). Constitutive CA125 production may vary with epithelial cell-cycle or differentiation state (36). MUC16 ectodomain cleavage can occur within acidifying Golgi/post-Golgi compartments, providing a potential inflammation-independent route for shedding (37). Because this cleavage pathway was demonstrated in other cell systems, its relevance to endometrial cancer remains to be established. Inflammation may therefore amplify MUC16 expression or CA125 release but is not required for basal expression and release. The endometrial-cancer-specific regulation of constitutive MUC16 shedding remains incompletely defined.

Recent endometrial cancer models showed that cell-associated MUC16 stabilized ESR1 and activated PI3K/AKT signaling, promoting proliferation, migration, invasion and xenograft growth (38). These findings support a potential functional role for membrane-associated MUC16 in tumor progression, but they do not establish that circulating CA125 has the same activity. Serum CA125 measurements in the present study therefore cannot determine the activity of the membrane-associated fraction.

The metabolic findings point to a different issue: Factors involved in endometrial cancer occurrence are not necessarily markers of an aggressive pathological phenotype. Obesity, insulin resistance, chronic inflammation and lipid metabolic abnormalities have well-established biological association with endometrial cancer development (22,23,31). Those occurrence-level associations, however, cannot be directly translated into a unidirectional signal of postoperative high-risk pathology. In the present study, the proportion of patients with BMI ≥25 kg/m^2 was lower in the composite high-risk group than in the non-high-risk group. This direction is consistent with previous evidence associating higher BMI to progesterone receptor positivity, endometrioid histology and other clinicopathological markers of non-aggressive disease (24). BMI distribution may also vary by molecular background (25). Even so, the pattern was not reproduced consistently across individual high-risk pathological factors. Diabetes, hypertension, metabolic syndrome and most lipid indicators likewise did not form a stable association pattern. The association between metabolic status and pathological behavior in endometrial cancer may therefore depend on histopathological and molecular context. The present data do not support BMI or routine metabolic indicators as standalone markers for identifying aggressive pathological status.

The molecular findings add context. The high-risk pathological phenotype observed in the present study should not be viewed as a single clinicopathological process. TCGA, ProMisE and Post-Operative Radiation Therapy in Endometrial Carcinoma studies have shown that molecular classification refines prognostic assessment beyond conventional histopathology and has become central to adjuvant-treatment discussions (4-10). In the present cohort, p53abn tumors were enriched among patients with the high-risk pathological phenotype, in keeping with the established association between p53 abnormality and aggressive pathological behavior. Differences in BMI and CA125 across molecular subtypes further suggest that the clinical meaning of routine indicators may vary by molecular background. Molecular-classification coverage was incomplete, and statistical evidence was attenuated after FDR correction. Accordingly, the molecular analyses provide exploratory context for interpreting CA125 across biologically distinct tumor subgroups.

Several limitations should be considered. The present study was retrospective and single-center, with a limited sample size, small event numbers for some individual pathological endpoints and incomplete molecular and metabolic data. Molecular testing was performed after individual clinician-patient discussion and was not completed in all patients; thus, molecular information was unavailable for complete risk stratification in part of the cohort. Although observed selection-bias assessment and sensitivity analyses were performed, unmeasured confounding and missing-data-related bias cannot be excluded and the main multivariable model adjusted only for selected clinical variables. All patients underwent systematic lymphadenectomy because the institutional sentinel lymph-node mapping and ultrastaging pathway was not available during the cohort period. This differs from contemporary sentinel lymph-node-based staging (39) and may influence the detection of low-volume nodal metastases, thereby limiting direct generalizability to cohorts assessed using sentinel lymph-node mapping with ultrastaging. Finally, recurrence, progression-free survival and overall survival were not prespecified outcomes, and follow-up was not sufficiently mature or uniform for reliable time-to-event analysis. Accordingly, the present study does not establish prognostic performance or treatment benefit, and it did not evaluate the incremental utility of CA125 within a formal clinical model.

In conclusion, higher preoperative CA125, particularly log(CA125), was associated with the prespecified composite adverse pathological phenotype after multivariable adjustment. The most consistent exploratory associations involved LVSI positivity and lymph node metastasis. BMI, diabetes, hypertension, metabolic syndrome and routine lipid indicators showed no reproducible associations with the composite outcome. Preoperative CA125 may therefore provide complementary risk information in real-world settings where molecular classification is incomplete. External validation in larger cohorts with complete molecular classification and prespecified clinical outcomes is required.

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Availability of data and materials

The datasets generated in the present study are not publicly available as they contain de-identified but potentially sensitive patient-level clinical information from hospital medical records but may be requested from the corresponding author with approval from the Institutional Review Board of Cangzhou Central Hospital Affiliated to Hebei Medical University.

Authors' contributions

YW and ShiL conceived and designed the study. YW performed the statistical analysis and drafted the manuscript. YY, WS, YG, BQ and XL collected and verified the clinical, laboratory and pathological data. ShoL contributed to data interpretation and methodological review. ShiL supervised the study, provided administrative and clinical guidance and critically revised the manuscript. YW and ShiL confirm the authenticity of all raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the principles of the Declaration of Helsinki and was reviewed and approved by the Institutional Review Board of Cangzhou Central Hospital Affiliated to Hebei Medical University (approval no. 2026-154-01). The requirement for informed consent was waived by the Institutional Review Board. Accordingly, therefore neither written nor oral informed consent was obtained. All data used for analysis were de-identified before statistical processing.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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