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Original Article

A predictive model based on BRCA1/2, POLE, TP53, and MSH6 mutations for immunotherapy response in advanced endometrial cancer

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Abstract: Objective: To evaluate clinical, molecular, and immunological predictors of response to immunotherapy among patients with advanced endometrial cancer and to develop a combined biomarker model for predicting treatment outcomes. Methods: This retrospective case-control study included 590 advanced endometrial cancer patients treated at the Affiliated Hospital of Hebei University of Engineering between December 2024 and May 2025. Eligible women underwent total hysterectomy, pelvic lymph node dissection, and received immune checkpoint inhibitors alongside standard chemotherapy. Patients were stratified into good and poor response groups based on 1-year post-treatment prognosis and response evaluation criteria in solid tumors. Baseline blood biomarkers, gene mutation status (breast cancer gene [BRCA] 1, BRCA2, DNA polymerase epsilon, tumor protein p53 [TP53], mutS homolog 6), and immunophenoscore (IPS) were assessed. Logistic regression and receiver operating characteristic (ROC) analyses were performed. A random forest model was constructed for combined biomarker prediction. Results: No significant differences in baseline demographic or clinical characteristics were found between response groups. Good responders had significantly lower baseline levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), neutrophil-lymphocyte ratio (NLR), cancer antigen 125 (CA125), and IPS, and higher frequencies of gene mutations. Multivariate regression identified elevated CRP, IL-6, TNF-α, NLR, CA125, and IPS as independent predictors of poor response; BRCA2 and TP53 mutations were independently associated with favorable outcomes. The combined biomarker model achieved an area under the ROC curve of 0.812, demonstrating strong predictive accuracy. Conclusion: Inflammatory and tumor biomarkers, IPS, and specific gene mutations are independently associated with immunotherapy response in advanced endometrial cancer. A combined biomarker model may enhance the prediction of treatment outcomes and guide individualized therapy.

Keywords: Endometrial cancer, immunotherapy, biomarkers, gene mutations, inflammatory markers, predictive model

Introduction

Endometrial cancer is the most common malignancy of the female reproductive tract in industrialized countries, with an incidence that has steadily increased over recent decades [1]. Although early-stage disease is often curable with surgery and adjuvant therapy, advanced and recurrent endometrial cancer presents a significant clinical challenge due to its poor prognosis and limited responsiveness to conventional treatments [2]. The emergence of immunotherapy, particularly immune checkpoint inhibitors (ICIs) targeting the programmed death 1 (PD-1) pathway and its ligands, has provided new therapeutic opportunities for subsets of patients with advanced endometrial cancer [3]. However, the heterogeneity in responses observed in clinical practice underscores the urgent need for reliable biomarkers to predict therapeutic benefit and guide personalized treatment strategies [4].

Recent advances in cancer genomics have highlighted the importance of genetic alterations in shaping the tumor microenvironment

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and modulating immune responses [5]. Among these, mutations in genes responsible for DNA repair and genomic stability - such as breast cancer gene (BRCA) 1, BRCA2, DNA polymerase epsilon (POLE), tumor protein p53 (TP53), and mutS homolog 6 (MSH6) - are of particular interest [6]. These genes are involved in critical processes, including homologous recombination, mismatch repair (MMR), and maintenance of genomic integrity. Deficiencies resulting from such mutations can lead to increased tumor mutational burden (TMB), emergence of neoantigens, and subsequently heightened tumor immunogenicity [7]. Notably, endometrial tumors with POLE exonuclease domain mutations or MMR deficiency, frequently involving MSH6, have demonstrated robust responses to ICIs in several clinical studies [7, 8]. BRCA1/2 and TP53 mutations, while more extensively characterized in other gynecologic malignancies, are less well-defined in the context of immunotherapeutic response in endometrial cancer [9].

Despite these promising observations, the relationship between the mutational landscape of endometrial cancer and clinical outcomes following immunotherapy remains incompletely understood. Most existing studies have focused on populations with known microsatellite instability (MSI) or POLE-mutated status, with limited evaluation of the full spectrum of relevant gene alterations [10]. There is also a paucity of large-scale, clinicopathologically annotated studies examining the correlation between specific gene mutations, inflammatory biomarkers, serological biomarkers and immunotherapy efficacy in real-world settings [11].

Given this context, we conducted a retrospective case-control study to comprehensively analyze the impact of BRCA1/2, POLE, TP53, and MSH6 mutations on the response to PD-1 inhibitor-based immunotherapy in patients with advanced endometrial cancer. In addition, we assessed a panel of blood-based biomarkers and integrated clinical data to delineate independent predictors of immunotherapy outcomes. By elucidating the interplay between genetic alterations and immunological parameters, our study aims to enhance the understanding of individual variability in treatment response and inform precision oncology approaches for this challenging disease.

Materials and methods

Case selection

Patient: This retrospective case-control study included 590 advanced endometrial cancer patients admitted to the Affiliated Hospital of Hebei University of Engineering from December 2024 to May 2025 as the research subjects. Demographic information of patients was collected through the case system. All procedures involving human participants in this study comply with the Helsinki Declaration. This study has been approved by the Ethics Committee of the Affiliated Hospital of Hebei University of Engineering. The use of de-identified patient data in this retrospective study posed no risk to patients; therefore, informed consent was waived.

Inclusion and exclusion criteria: Inclusion criteria: (1) Women aged 18 or above; (2) Diagnosis of advanced endometrial cancer [12]; (3) Treatment with ICIs; (4) Clear records of BRCA1/2, POLE, TP53, and MSH6 gene mutation status; (5) No prior history of other malignancies within the last five years; (6) Eastern Cooperative Oncology Group performance status of 0-2.

Exclusion criteria: (1) Radiation chemotherapy prior to admission; (2) Known mutation status before diagnosis; (3) Hematological or immune system diseases; (4) Mental-illness-induced difficulty in cooperating with treatment and examination; (5) Incomplete case records and follow-up data; (6) Pregnant or breastfeeding women; (7) Active infections requiring systemic antibiotic treatment.

Grouping criteria: We recorded the patient's prognosis within one year after surgery and evaluated the efficacy of observation indicators based on the Response Evaluation Criteria in Solid Tumors [13]. This study divided patients into good response group (n = 123) and poor response group (n = 467) based on their response to immunotherapy. Patients with progressive disease (PD) or death were included in the poor response group, while patients with complete response (CR), partial response (PR), and stable disease (SD) were included in the good response group. CR: The lesion disappears completely and lasts for more than 1 month; PR: The total maximum diameter of the

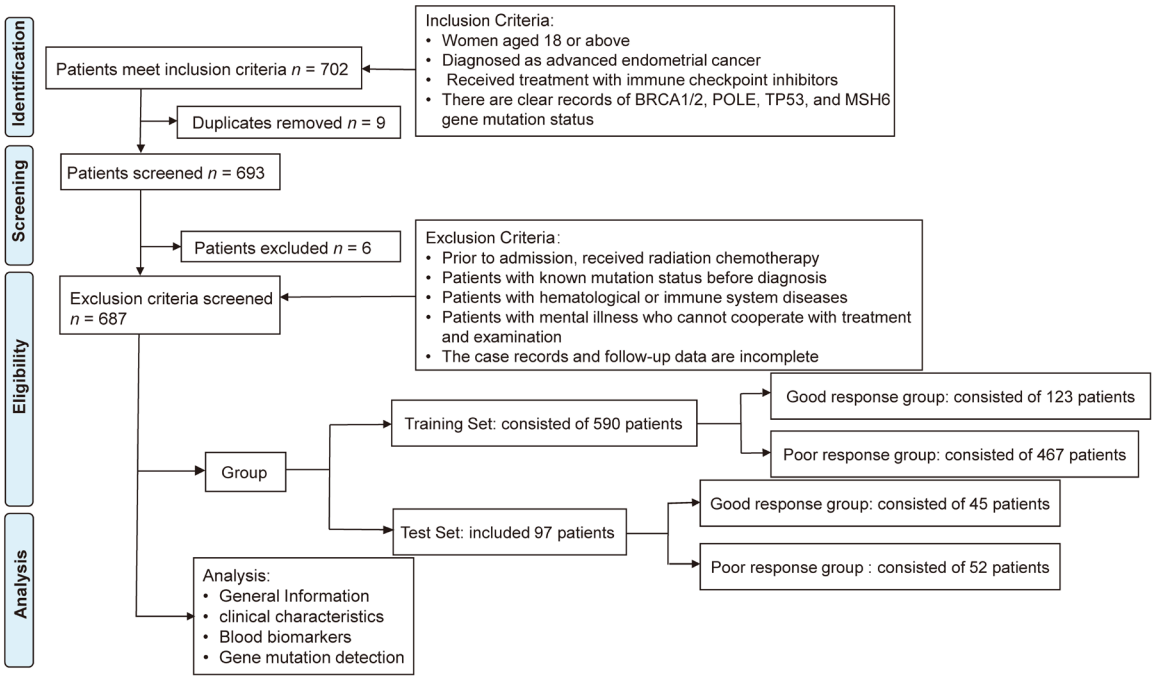

Figure 1. Research and design flowchart. Note: BRCA1/2: Breast Cancer 1/2; POLE: DNA Polymerase Epsilon; TP53: Tumor Protein P53; MSH6: MutS Homolog 6.

lesion decreased by ≥ 30% compared to the pre-treatment measurement, with a duration of > 1 month; SD: The total change in the maximum diameter of the lesion is between partial remission and progression; PD: The total maximum diameter of lesions increases by ≥ 20% compared to the pre-treatment measurement, or new lesions appear. Additionally, this study used a 10-fold cross-validation method for the internal validation of the predictive model to ensure its stability and reliability. Furthermore, 97 patients who met the same inclusion criteria were included in the external validation. According to the Response Evaluation Criteria in Solid Tumors, the external validation was also divided into a good response group (n = 45) and a poor response group (n = 52) (**Figure 1**).

Treatment methods

Sintilimab (2072873-06-2, Macklin, China) was administered intravenously at a dose of 200 mg over approximately 30-60 minutes on day 1 of each cycle. Fruquintinib (H20180015, Hutchison Whampoa, China) was given orally at a dose of 5 mg once daily from day 1 to day 14 of each cycle, followed by a break in medication from day 15 to day 21. On the first day of chemotherapy, patients received Paclitaxel (ab120143, Abcam, USA) via intravenous infusion at a dose of 175 mg per square meter of body surface area over 3 hours, along with Carboplatin (H10920028, Qilu Pharmaceutical Co., China) dosed at 5 mg/mL/min for 30 to 60 minutes. Each cycle lasted for 21 days until disease progression or the occurrence of intolerable toxicity.

Data collection and outcome measurement

Blood testing: Blood testing included the measurement of inflammatory markers, tumor related biomarkers, and immune parameters. Fasting venous blood (6 ml) was collected from the patient, and then it was centrifuged at 3000 rpm for 10 minutes at 4°C. The upper serum was used for the following tests.

Enzyme-linked immunosorbent assay was used to detect C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), cancer antigen 125 (CA125), and human epididymal protein 4 (HE4). The reagent kits used in this process were CRP (ab260058, Abcam, USA), IL-6 (ab178013, Abcam, USA), TNF-α (ab181421, Abcam, USA), CA125 (ab274402, Abcam, USA), HE4 (ab240688, Abcam, USA).

Sysmex XN-1000 analyzer (Sysmex, Japan) was used to detect the neutrophil, lymphocyte, and white blood cells counts of ethylenediaminetetraacetic acid (ab93684, Abcam, USA) anticoagulant blood samples, and to calculate the neutrophil-lymphocyte ratio (NLR) for each patient. Lactate dehydrogenase (LDH) activity and cerebrospinal fluid (CSF) glucose concentration were measured using Hitachi 7600 series fully automated biochemical analyzer (Hitachi High-Tech Corporation, Japan) and specialized CSF kit (Roche Diagnostics GmbH, Germany). Natural killer (NK) cells and T cells (cluster of differentiation 3 positive [CD3+] cells) were assessed using flow cytometry with a BD FACSCalibur flow cytometer (BD Biosciences, USA). Lymphocyte subsets were identified using monoclonal antibodies conjugated to fluorochromes, including anti-CD3 fluorescein isothiocyanate and anti-CD16/CD56 phycoerythrin (BD Biosciences, USA).

Gene mutation detection: The Formalin-Fixed Paraffin-Embedded samples of tumor tissue were sent to Zhongshan TopGene Clinical Diagnostic Laboratory (China). Genomic DNA was extracted from each sample using the Mag-Bind Blood & Tissue DNA HDQ 96 Kit (M6399-00, Omega Bioservices, USA). Ultraviolet spectrophotometer (ND-3300, Thermo Fisher Scientific, USA) was used to check DNA quality. Fluorescence spectrometer (Q33218, Thermo Fisher Scientific, USA) was employed for DNA quantification. Target sequences from extracted DNA was captured using a customized panel (TopGene, China). The polymerase chain reaction products were subjected to quality inspection using LabChip GX Touch nucleic acid analyzer (CLS138162, PerkinElmer, USA). The NextSeq CN500 platform (Illumina, USA) was used for end-to-end sequencing to detect mutations in BRCA1/2, POLE, TP53, and MSH6. The average depth of each sample was at least 300×, and the read length was 2×150 bp.

Immunophenoscore (IPS) analysis: The IPS algorithm of patients with endometrial cancer was retrieved from the Cancer Immunome Atlas (https://tcia.at/home), which reflects patients' capability to respond to ICIs. Immunosuppressive cells, effector cells, major histocompatibility complex (MHC) molecules, and immunomodulators were defined as the four components of IPS. IPS relies on gene expression data obtained through high-throughput technologies. The method primarily involves isolating total RNA from tissues or cells, reversely transcribing it into cDNA, adding sequencing adapters, sequencing using the Illumina platform, aligning the reads to the reference genome with tools such as STAR or HISAT2, and finally calculating the expression levels using Fragments Per Kilobase Million. To standardize the expression levels of representative genes for four types of immune components, Z-score normalization was used (formula: $Z = (X - \mu)/\sigma$, where X is the gene expression value, μ is the mean, and σ is the standard deviation). The Z-score of stimulatory factors (effector cells, MHC molecules, immunomodulators) is positively weighted. The Z-score of inhibitory factors (immunosuppressive cells) is negatively weighted. The comprehensive Z-score is calculated as $[\sum(Wstim \cdot Zstim) - \sum(Wsupp \cdot Zsupp)]/N$, where W represents the weight and Z represents the Z-score. The Z-score was converted to a 0-10 Immune Profile Score (IPS) scale as follows: If Z-score ≥ 3, then IPS = 10; If Z-score ≤ 0, then IPS = 0; For $0 <$ Z-score < 3, the IPS was calculated by linear mapping. For instance, if Z-score = 1.5, then IPS = 5. The scale of the IPS ranged from 0-10 and was determined by summing the corresponding gene expression scores, whereby higher scores were positively associated with increased immunogenicity.

Statistical method

The data analysis was conducted using SPSS 29.0 statistical software (SPSS Inc., Illinois, USA). Classification data is represented in the format of [n (%)] and was analyzed using chi-square (χ^2) tests or Fisher's exact test where appropriate. For continuous data with normal distribution, the results are expressed as ($X \pm s$) and compared using t-test. Pearson correlation analysis was used for continuous variables, and Spearman correlation analysis was used for categorical variables. To evaluate the association between glucose and lipid metabolism parameters and treatment response in patients with glioblastoma and metabolic syndrome, univariate and multivariate logistic regression analyses were conducted. Univariate logistic regression analysis was used to evaluate the independent effects of BRCA1/2, POLE, TP53, and MSH6 mutations on immune therapy response. Variables that showed statistical sig-

Table 1. Comparison of general information between two groups

Parameters	Good response group (n = 123)	Poor response group (n = 467)	t/χ^2	p
Age (years)	51.74 ± 6.65	52.86 ± 7.44	1.521	0.129
BMI (kg/m^2)	25.02 ± 3.00	24.73 ± 3.30	0.866	0.387
Education Level [n (%)]			0.193	0.908
Primary or Below	27 (21.95%)	102 (21.84%)		
Secondary School	61 (49.59%)	223 (47.75%)		
College or Above	35 (28.46%)	142 (30.41%)		
Employment Status [n (%)]			0.241	0.623
Employed	77 (62.6%)	281 (60.17%)		
Unemployed	46 (37.4%)	186 (39.83%)		
Marital Status [n (%)]			0.002	0.969
Married	105 (85.37%)	398 (85.22%)		
Divorced	18 (14.63%)	69 (14.78%)		
Current Residence [n (%)]			1.224	0.269
Rural	55 (44.72%)	235 (50.32%)		
Urban	68 (55.28%)	232 (49.68%)		
Hypertension [n (%)]			3.708	0.054
Yes	77 (62.6%)	247 (52.89%)		
No	46 (37.4%)	220 (47.11%)		
Diabetes [n (%)]			1.023	0.312
Yes	21 (17.07%)	99 (21.2%)		
No	102 (82.93%)	368 (78.8%)		
Smoking [n (%)]			4.009	0.135
Never	113 (91.87%)	449 (96.15%)		
Former	6 (4.88%)	10 (2.14%)		
Current	4 (3.25%)	8 (1.71%)		
Drinking [n (%)]			0.348	0.840
Never	72 (58.54%)	287 (61.46%)		
Former	15 (12.2%)	53 (11.35%)		
Current	36 (29.27%)	127 (27.19%)		

Note: BMI: Body Mass Index.

nificance in univariate analysis were subsequently included in a multiple logistic regression model to adjust for potential confounding factors and determine independent predictors of treatment response. The results of logistic regression analysis are expressed as the odds ratio (OR) along with its 95% confidence interval and the corresponding *P*-value. A *P*-value < 0.05 is considered statistically significant.

Results

Comparison of general information between two groups

In this study cohort, there were no statistically significant differences in age, body mass index, education level, employment status, marital status, current residence, hypertension, diabetes, smoking, or drinking status between the good and poor response groups (all P > 0.05) (**Table 1**). These findings indicated that the two groups were generally well balanced in baseline demographic and clinical characteristics.

Comparison of clinical characteristics between two groups

There were no significant differences between the good response group and the poor response group in terms of disease duration, cancer type, histological subtype, histologic grade, peritoneal cytology, or previous revascularization history (all P > 0.05) (**Table 2**). The mean

Table 2. Comparison of clinical characteristics between two groups

Parameters	Good response group (n = 123)	Poor response group (n = 467)	t/χ^2	p
Disease Duration (months)	6.32 ± 2.59	6.48 ± 2.67	0.573	0.567
Cancer Type [n (%)]			0.448	0.503
Type I Endometrial Cancer	113 (91.87%)	437 (93.58%)		
Type II Endometrial Cancer	10 (8.13%)	30 (6.42%)		
Histological Subtype [n (%)]			0.989	0.320
Endometrioid Type	91 (73.98%)	324 (69.38%)		
Non-Endometrioid Type	32 (26.02%)	143 (30.62%)		
Histologic Grade [n (%)]			0.389	0.533
Stage III	67 (54.47%)	269 (57.6%)		
Stage IV	56 (45.53%)	198 (42.4%)		
Peritoneal Cytology [n (%)]			0.064	0.801
Negative	73 (59.35%)	283 (60.6%)		
Positive	50 (40.65%)	184 (39.4%)		
Previous Revascularization History [n (%)]			2.262	0.133
PCI	61 (49.59%)	234 (50.11%)		
CABG	62 (50.41%)	233 (49.89%)		
Prognosis Conditions [n (%)]			590.000	< 0.001
CR	29 (23.58%)	\		
PR	42 (34.15%)	\		
SD	52 (42.28%)	\		
PD	\	309 (66.17%)		
Mortality	\	158 (33.83%)		

Note: PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease.

disease duration was similar between both groups. Type I endometrial cancer was predominant in both groups, while the distributions of endometrioid and non-endometrioid histology, as well as stage III and IV disease, were similar. Peritoneal cytology status and history of percutaneous coronary intervention or coronary artery bypass grafting showed no significant differences between groups. Regarding prognosis, all patients in the good response group had CR, PR, or SD, while all patients in the poor response group experienced PD or mortality ($P < 0.001$). These results demonstrated that the primary clinical characteristics were comparable between groups, and significant differences were observed only in response outcomes.

Comparison of blood biomarkers between two groups

At baseline, patients in the good response group exhibited significantly lower levels of serum CRP ($P = 0.003$), IL-6 ($P = 0.022$), TNF-α ($P = 0.001$), and NLR ($P = 0.004$) compared with the poor response group. Similarly, CA125 levels were lower in the good response group than in the poor response group ($P = 0.013$). The good response group also demonstrated a significantly lower IPS compared to the poor response group ($P < 0.001$). No significant differences were observed between the groups in baseline concentrations of neutrophils, lymphocytes, white blood cells, HE4, LDH, CSF glucose, percentages of NK cells, or CD3+ T cells (**Table 3**).

Comparison of gene mutation detection between two groups

Patients in the good response group exhibited significantly higher frequencies of gene mutations compared with the poor response group, including BRCA1 ($P = 0.017$), BRCA2 ($P = 0.017$), POLE ($P = 0.042$), TP53 ($P = 0.002$), and MSH6 ($P = 0.015$) (**Table 4**). The distributions of wild-type alleles for each gene were

Table 3. Comparison of blood biomarkers between two groups

Parameters	Good response group (n = 123)	Poor response group (n = 467)	t	p
Serum Inflammatory Cytokine				
CRP (mg/L)	6.47 ± 3.35	7.12 ± 0.26	3.044	0.003
IL-6 (pg/mL)	13.96 ± 6.67	15.41 ± 0.67	2.314	0.022
TNF-α (pg/mL)	12.53 ± 5.77	14.28 ± 2.72	3.273	0.001
Neutrophil (1×10^3/μL)	4.32 ± 1.06	4.37 ± 1.08	0.425	0.671
Lymphocyte (1×10^3/μL)	2.03 ± 0.68	2.09 ± 0.71	0.880	0.379
White Blood Cell (1×10^3/μL)	7.38 ± 1.62	7.56 ± 1.67	1.064	0.288
NLR	2.91 ± 1.12	3.21 ± 0.11	2.938	0.004
Tumor Markers				
CA125 (IU/mL)	22.52 ± 9.35	24.65 ± 3.67	2.516	0.013
HE4 (pmol/L)	77.17 ± 11.41	77.87 ± 12.57	0.564	0.573
LDH (U/L)	219.83 ± 62.25	231.23 ± 48.47	1.887	0.061
CSF Glu (mmol/L)	2.96 ± 1.19	3.14 ± 0.35	1.724	0.087
Immunological Parameters				
NK Cells [n (%)]	12.55 ± 3.58	12.24 ± 3.62	0.852	0.395
CD3+ T Cells [n (%)]	67.51 ± 8.47	67.34 ± 8.52	0.201	0.841
IPS (score)	6.92 ± 0.91	7.24 ± 0.56	3.724	< 0.001

Note: CRP: C-Reactive Protein; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor alpha; NLR: Neutrophil-Lymphocyte Ratio; CA125: Cancer Antigen 125; HE4: Human Epididymal Protein 4; LDH: Lactate Dehydrogenase; CSF Glu: Cerebrospinal Fluid Glucose; NK Cells: Natural Killer Cells; CD3+ T Cells: Cluster of Differentiation 3 Positive T Lymphocytes; IPS: Immunophenoscore.

Table 4. Comparison of gene mutation detection between two groups

Parameters	Good response group (n = 123)	Poor response group (n = 467)	χ^2	p
BRCA1 [n (%)]			5.736	0.017
Mutant Type	23 (18.70%)	50 (10.71%)		
Wild Type	100 (81.30%)	417 (89.29%)		
BRCA2 [n (%)]			5.717	0.017
Mutant Type	24 (19.51%)	53 (11.35%)		
Wild Type	99 (80.49%)	414 (88.65%)		
POLE [n (%)]			4.118	0.042
Mutant Type	16 (13.01%)	34 (7.28%)		
Wild Type	107 (86.99%)	433 (92.72%)		
TP53 [n (%)]			9.918	0.002
Mutant Type	60 (48.78%)	156 (33.40%)		
Wild Type	63 (51.22%)	311 (66.60%)		
MSH6 [n (%)]			5.877	0.015
Mutant Type	20 (16.26%)	41 (8.78%)		
Wild Type	103 (83.74%)	426 (91.22%)		

Note: BRCA1: Breast Cancer 1; BRCA2: Breast Cancer 2; POLE: DNA Polymerase Epsilon; TP53: Tumor Protein 53; MSH6: MutS Homolog 6.

correspondingly lower in the good response group than in the poor response group. These findings suggest that mutations in BRCA1, BRCA2, POLE, TP53, and MSH6 are more prevalent among advanced endometrial cancer patients who exhibit a favorable response to immunotherapy.

Correlation analysis between biomarkers and immunotherapy response

Correlation analysis revealed that higher levels of CRP (rho = 0.119, P = 0.004), IL-6 (rho = 0.117, P = 0.005), TNF-α (rho = 0.153, P < 0.001), NLR (rho = 0.185, P < 0.001), CA125

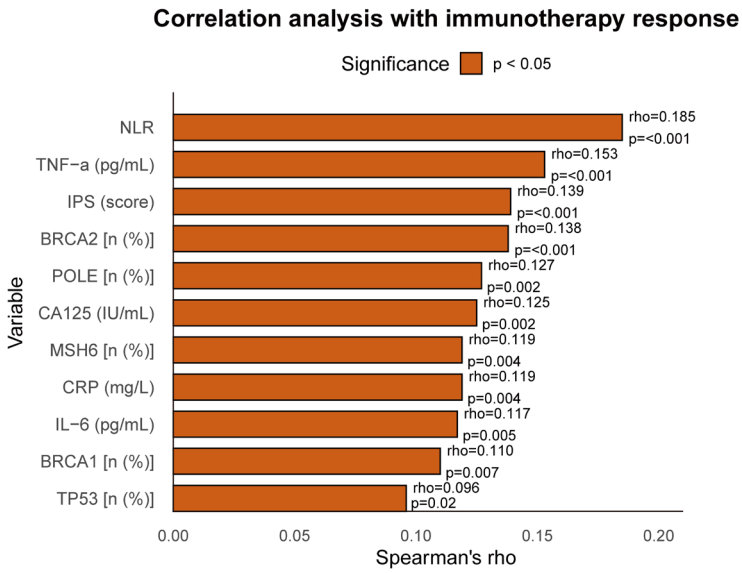

Figure 2. Correlation analysis between various variables and immunotherapy response. Note: CRP: C-Reactive Protein; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor alpha; NLR: Neutrophil-Lymphocyte Ratio; CA125: Cancer Antigen 125; IPS: Immunophenoscore; BRCA1: Breast Cancer 1; BRCA2: Breast Cancer 2; POLE: DNA Polymerase Epsilon; TP53: Tumor Protein 53; MSH6: MutS Homolog 6.

(rho = 0.125, P = 0.002), and IPS (rho = 0.139, P < 0.001) were significantly associated with immunotherapy response in patients with advanced endometrial cancer. In addition, mutations in BRCA1 (rho = 0.110, P = 0.007), BRCA2 (rho = 0.138, P < 0.001), POLE (rho = 0.127, P = 0.002), TP53 (rho = 0.096, P = 0.020), and MSH6 (rho = 0.119, P = 0.004) also demonstrated significant positive correlations with response to immunotherapy (**Figure 2**). These findings indicate that both specific inflammatory and tumor biomarkers, as well as gene mutations, are significantly correlated with immunotherapy outcomes.

Regression analysis of immunotherapy response

For CRP, we selected 7 mg/L as the cutoff point (≤ 7 mg/L vs. > 7 mg/L), as this level is often considered the threshold for distinguishing between low-grade and high-grade inflammatory states. For IL-6, we adopted 15 pg/mL as the cutoff value (≤ 15 pg/mL vs. > 15 pg/mL), based on observations that this level effectively distinguishes differences in patients' immune responses. For TNF-α, we used 14 pg/mL as the cutoff value (≤ 14 pg/mL vs > 14 pg/mL), a standard frequently employed to assess the degree of inflammatory response. For NLR, we used 3 as the cutoff value (≤ 3 vs > 3), based on clinical consensus that an NLR greater than 3 is often associated with adverse prognosis. For CA125, we selected 24 IU/mL as the cutoff value (≤ 24 IU/mL vs > 24 IU/mL), a standard commonly used to differentiate between normal ranges and abnormal elevations. For IPS, we used 7 as the cutoff value (≤ 7 vs > 7), because this score has been shown to be an effective threshold for distinguishing different immune phenotypes. Multivariate regression analysis identified elevated baseline levels of CRP (OR, 1.500; P < 0.001), IL-6 (OR, 1.072; P = 0.008), TNF-α (OR, 1.130; P < 0.001), NLR (OR, 2.046; P < 0.001), CA125 (OR, 1.083; P = 0.002), and IPS (OR, 2.280; P < 0.001) as independent risk factors for poor immunotherapy response in advanced endometrial cancer (**Table 5**). Among gene mutations, BRCA2 (OR, 0.435; P = 0.010) and TP53 (OR, 0.537; P = 0.009) were independently associated with a favorable response, whereas BRCA1, POLE, and MSH6 mutations did not remain significant in multivariate analysis. These results highlight the importance of both inflammatory biomarkers and specific gene mutations in predicting immunotherapy outcomes.

Receiver Operating Characteristic (ROC) curve analysis of key indicators

ROC analysis demonstrated that among the studied parameters, IPS achieved the highest area under the curve (AUC) at 0.599, followed by CA125 (AUC, 0.588). CRP, IL-6, TNF-α, and NLR had similar AUCs of 0.575, 0.559, 0.565, and 0.558, respectively, with moderate specificities but relatively low sensitivities (**Figure 3**). All gene mutations, including BRCA1, BRCA2, POLE, TP53, and MSH6, exhibited low AUCs (all < 0.50) with high specificities (0.857-0.869) but consistently low sensitivities (0.228-0.268), and limited discriminative performance as indicated by low Youden indexes and F1

Table 5. Regression analysis of immunotherapy response

Parameters	Univariate analysis			Multivariate analysis		
	p	OR	95% CI	p	OR	95% CI
CRP (≤ 7 mg/L/> 7 mg/L)	< 0.001	1.619	1.358-1.950	< 0.001	1.500	1.224-1.839
IL-6 (≤ 15 pg/mL/> 15 pg/mL)	0.002	1.076	1.028-1.126	0.008	1.072	1.019-1.129
TNF-α (≤ 14 pg/mL/> 14 pg/mL)	< 0.001	1.139	1.078-1.205	< 0.001	1.130	1.063-1.202
NLR (≤ 3/> 3)	< 0.001	2.798	1.904-4.238	< 0.001	2.046	1.344-3.114
CA125 (≤ 24 IU/mL/> 24 IU/mL)	< 0.001	1.113	1.064-1.168	0.002	1.083	1.030-1.139
IPS (≤ 7 score/> 7 score)	< 0.001	2.120	1.552-2.930	< 0.001	2.280	1.586-3.276
BRCA1 (Mutant Type/Wild Type)	0.018	0.521	0.307-0.907	0.064	0.545	0.287-1.036
BRCA2 (Mutant Type/Wild Type)	0.018	0.528	0.314-0.909	0.010	0.435	0.231-0.818
POLE (Mutant Type/Wild Type)	0.045	0.525	0.284-1.009	0.078	0.517	0.249-1.076
TP53 (Mutant Type/Wild Type)	0.002	0.527	0.352-0.788	0.009	0.537	0.338-0.853
MSH6 (Mutant Type/Wild Type)	0.017	0.496	0.282-0.897	0.288	0.686	0.343-1.374

Note: OR: Odds Ratio; CI: Confidence Interval; CRP: C-Reactive Protein; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor alpha; NLR: Neutrophil-Lymphocyte Ratio; CA125: Cancer Antigen 125; IPS: Immunophenoscore; BRCA1: Breast Cancer 1; BRCA2: Breast Cancer 2; POLE: DNA Polymerase Epsilon; TP53: Tumor Protein 53; MSH6: MutS Homolog 6.

scores. Overall, these markers displayed only modest accuracy in distinguishing immunotherapy response in advanced endometrial cancer.

Development of a nomogram predictive model

As shown in **Figure 4**, a combined prediction model for biomarkers influencing immunotherapy response among patients with advanced endometrial cancer was established. We developed and validated a comprehensive nomogram (**Figure 4B**). The calibration curve (**Figure 4A**) indicated a close agreement between the predicted probabilities and the observed outcomes, demonstrating the reliability of our model. The out-of-bag error rate plot (**Figure 4C**) demonstrated model stability and efficiency across a range of decision trees. Variable importance analysis (**Figure 4D**) indicated that NLR, IL-6, TNF-α, CA125, and IPS were the most critical contributors to the predictive model. The ROC curve (**Figure 4E**) revealed that the combined model achieved a robust discriminative performance, with an AUC of 0.812, indicating strong capability in distinguishing responders from non-responders to immunotherapy based on these integrated biomarkers.

Comparison of parameters between two groups in the external validation set

In the external validation set, we compared various parameters between the good response group (n = 45) and the poor response group (n = 52). There were no significant differences observed in demographic characteristics such as age, body mass index, education level, employment status, marital status, current residence, nor in disease-related factors including hypertension, diabetes, smoking habits, drinking habits, disease duration, cancer type, histology, histologic grade, peritoneal cytology, or previous revascularization procedures (percutaneous coronary intervention and coronary artery bypass grafting, all P > 0.05). Regarding prognosis, all patients in the good response group had CR, PR, or SD, while all patients in the poor response group experienced PD or mortality (P < 0.001). Levels of neutrophil count, lymphocyte count, white blood cell count, HE4, LDH, CSF glucose levels, NK cells percentage, and CD3+ T cells percentage did not show significant differences between groups (all P > 0.05). However, there were several markers that exhibited significant differences. CRP levels were significantly higher in the poor response group compared to the good response group (P = 0.015). IL-6 levels also showed significant increases in the poor response group (P = 0.035). TNF-α levels were significantly higher in the poor response group compared to the good response group (P = 0.048). NLR (P = 0.002) showed a significant increase in the poor response group. Additionally, CA125 levels (P = 0.043) and IPS score (P = 0.013) were higher in the poor response group. Genetic markers also displayed significant differences: BRCA1 (P = 0.022), BRCA2 (P

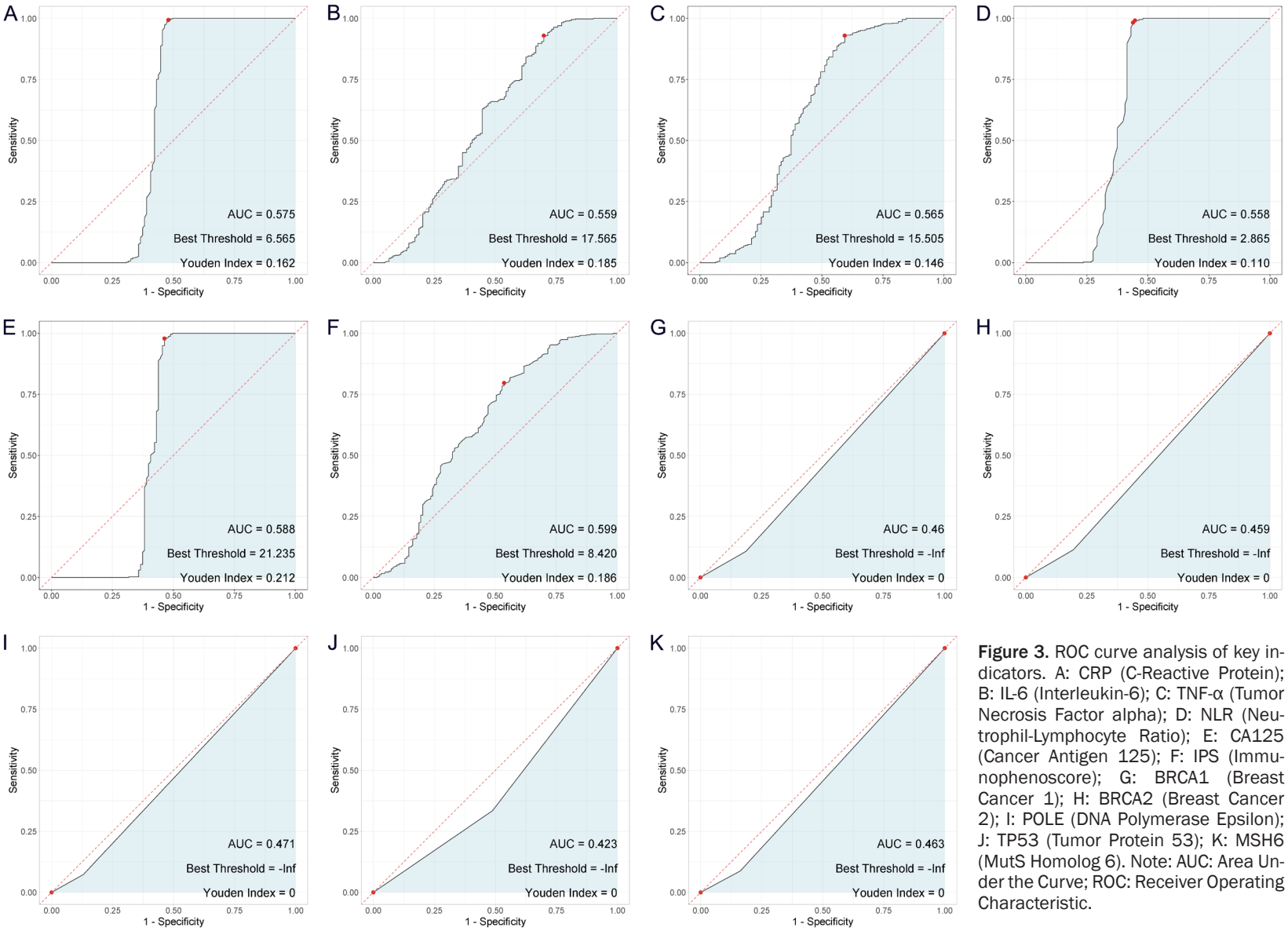

Figure 3. ROC curve analysis of key indicators. A: CRP (C-Reactive Protein); B: IL-6 (Interleukin-6); C: TNF-α (Tumor Necrosis Factor alpha); D: NLR (Neutrophil-Lymphocyte Ratio); E: CA125 (Cancer Antigen 125); F: IPS (Immunophenoscore); G: BRCA1 (Breast Cancer 1); H: BRCA2 (Breast Cancer 2); I: POLE (DNA Polymerase Epsilon); J: TP53 (Tumor Protein 53); K: MSH6 (MutS Homolog 6). Note: AUC: Area Under the Curve; ROC: Receiver Operating Characteristic.

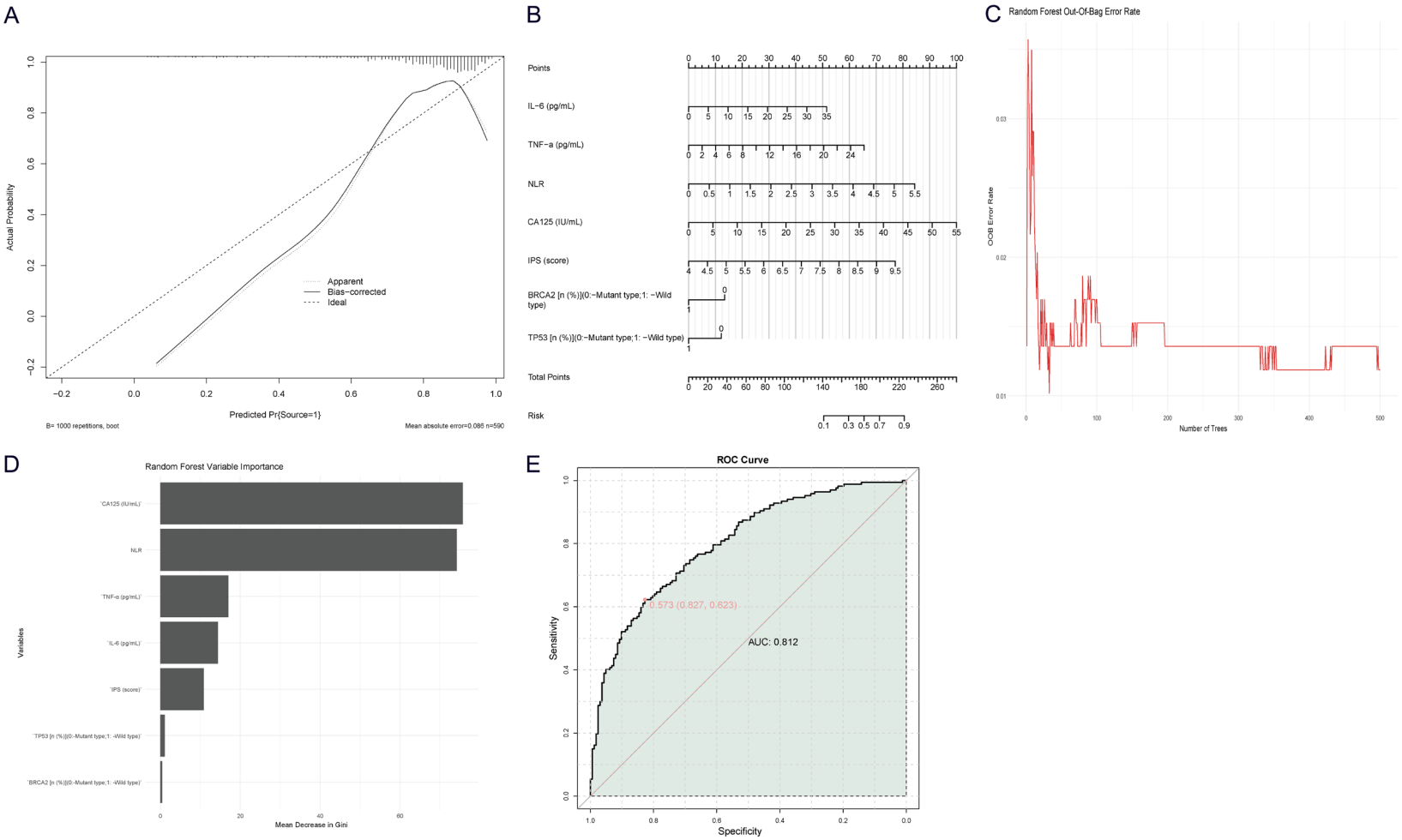

Figure 4. Development of a nomogram predictive model. A: Calibration curve; B: Nomogram; C: Out-of-bag error rate plot; D: Random forest variable importance; E: ROC curve. Note: ROC: Receiver Operating Characteristic; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor alpha; NLR: Neutrophil-Lymphocyte Ratio; CA125: Cancer Antigen 125; IPS: Immunophenoscore; BRCA2: Breast Cancer 2; TP53: Tumor Protein 53.

Table 6. Comparison of parameters between two groups in the external validation set

Parameters	Good response group (n = 45)	Poor response group (n = 52)	t/χ^2	p
Age (years)	50.52 ± 6.42	51.67 ± 7.73	0.793	0.430
BMI (kg/m^2)	25.56 ± 3.52	24.28 ± 3.32	1.846	0.068
Education Level [n (%)]			0.433	0.805
Primary or Below	10 (22.22%)	9 (17.31%)		
Secondary School	21 (46.67%)	27 (51.92%)		
College or Above	14 (31.11%)	16 (30.77%)		
Employment Status [n (%)]			0.275	0.600
Employed	30 (66.67%)	32 (61.54%)		
Unemployed	15 (33.33%)	20 (38.46%)		
Marital Status [n (%)]			0.750	0.386
Married	40 (88.89%)	43 (82.69%)		
Divorced	5 (11.11%)	9 (17.31%)		
Current Residence [n (%)]			0.107	0.743
Rural	21 (46.67%)	26 (50.00%)		
Urban	24 (53.33%)	26 (50.00%)		
Hypertension [n (%)]			2.164	0.141
Yes	30 (66.67%)	27 (51.92%)		
No	15 (33.33%)	25 (48.08%)		
Diabetes [n (%)]			0.742	0.389
Yes	8 (17.78%)	13 (25.00%)		
No	37 (82.22%)	39 (75.00%)		
Smoking [n (%)]			1.272	0.530
Never	42 (93.33%)	45 (86.54%)		
Former	2 (4.44%)	4 (7.69%)		
Current	1 (2.22%)	3 (5.77%)		
Drinking [n (%)]			0.058	0.971
Never	40 (88.89%)	47 (90.38%)		
Former	3 (6.67%)	3 (5.77%)		
Current	2 (4.44%)	2 (3.85%)		
Disease Duration (months)	6.25 ± 2.17	6.41 ± 2.86	0.312	0.756
Cancer type [n (%)]			0.341	0.559
Type I Endometrial Cancer	40 (88.89%)	49 (94.23%)		
Type II Endometrial Cancer	5 (11.11%)	3 (5.77%)		
Histology [n (%)]			2.187	0.139
Endometrioid Type	37 (82.22%)	36 (69.23%)		
Non-Endometrioid Type	8 (17.78%)	16 (30.77%)		
Histologic Grade [n (%)]			0.045	0.832
Stage III	25 (55.56%)	30 (57.69%)		
Stage IV	20 (44.44%)	22 (42.31%)		
Peritoneal Cytology [n (%)]			0.024	0.877
Negative	27 (60.00%)	32 (61.54%)		
Positive	18 (40.00%)	20 (38.46%)		
Previous Revascularization [n (%)]			0.058	0.810
PCI	24 (53.33%)	29 (55.77%)		
CABG	21 (46.67%)	23 (44.23%)		

Prognosis Conditions [n (%)]			97.000	< 0.001
CR	11 (24.44%)	\		
PR	13 (28.89%)	\		
SD	21 (46.67%)	\		
PD	\	31 (59.62%)		
Mortality	\	21 (40.38%)		
CRP (mg/L)	6.53 ± 2.12	7.37 ± 0.68	2.526	0.015
IL-6 (pg/mL)	13.42 ± 6.24	15.81 ± 4.37	2.148	0.035
TNF-α (pg/mL)	12.52 ± 5.21	14.21 ± 2.24	2.017	0.048
Neutrophil (1×10^3/μL)	4.41 ± 1.31	4.14 ± 1.04	1.149	0.253
Lymphocyte (1×10^3/μL)	2.05 ± 0.55	2.12 ± 0.63	0.600	0.550
White blood cell (1×10^3/μL)	7.42 ± 1.26	7.46 ± 1.42	0.137	0.891
NLR	2.41 ± 1.25	3.01 ± 0.14	3.228	0.002
CA125 (IU/mL)	22.27 ± 7.43	24.86 ± 4.25	2.061	0.043
HE4 (pmol/L)	77.51 ± 11.62	77.63 ± 12.52	0.048	0.962
LDH (U/L)	219.42 ± 62.26	231.63 ± 48.77	1.082	0.282
CSF Glu (mmol/L)	2.92 ± 1.36	3.23 ± 0.82	1.339	0.185
NK Cells [n (%)]	12.17 ± 3.88	12.52 ± 3.12	0.491	0.625
CD3+ T Cells [n (%)]	67.35 ± 8.54	67.74 ± 8.77	0.223	0.824
IPS (score)	6.92 ± 0.74	7.32 ± 0.81	2.527	0.013
BRCA1 [n (%)]			5.271	0.022
Mutant Type	16 (35.56%)	8 (15.38%)		
Wild Type	29 (64.44%)	44 (84.62%)		
BRCA2 [n (%)]			7.660	0.006
Mutant Type	17 (37.78%)	7 (13.46%)		
Wild Type	28 (62.22%)	45 (86.54%)		
POLE [n (%)]			13.774	< 0.001
Mutant Type	19 (42.22%)	5 (9.62%)		
Wild Type	26 (57.78%)	47 (90.38%)		
TP53 [n (%)]			5.969	0.015
Mutant Type	22 (48.89%)	13 (25.00%)		
Wild Type	23 (51.11%)	39 (75.00%)		
MSH6 [n (%)]			6.756	0.009
Mutant Type	15 (33.33%)	6 (11.54%)		
Wild Type	30 (66.67%)	46 (88.46%)		

Note: BMI: Body Mass Index; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; CRP: C-Reactive Protein; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor alpha; NLR: Neutrophil-Lymphocyte Ratio; CA125: Cancer Antigen 125; HE4: Human Epididymal Protein 4; LDH: Lactate Dehydrogenase; CSF Glu: Cerebrospinal Fluid Glucose; NK Cells: Natural Killer Cells; CD3+ T Cells: Cluster of Differentiation 3 Positive T Lymphocytes; IPS: Immunophenoscore; BRCA1: Breast Cancer 1; BRCA2: Breast Cancer 2; POLE: DNA Polymerase Epsilon; TP53: Tumor Protein 53; MSH6: MutS Homolog 6.

= 0.006), POLE (P < 0.001), TP53 (P = 0.015), and MSH6 (P = 0.009) mutation frequencies. In this external validation dataset, these results indicate that the significant differences between the two groups in prognosis conditions, CRP, IL-6, TNF-α, NLR, CA125, IPS score, and genetic mutations are consistent with the results of the test set (**Table 6**).

External validation ROC curve

The external validation ROC curve (**Figure 5**) demonstrated an AUC of 0.803, indicating a strong predictive ability of the model. The optimal cut-off point was identified at 0.470 with a sensitivity of 0.644 and specificity of 0.885. These results suggest that the significant dif-

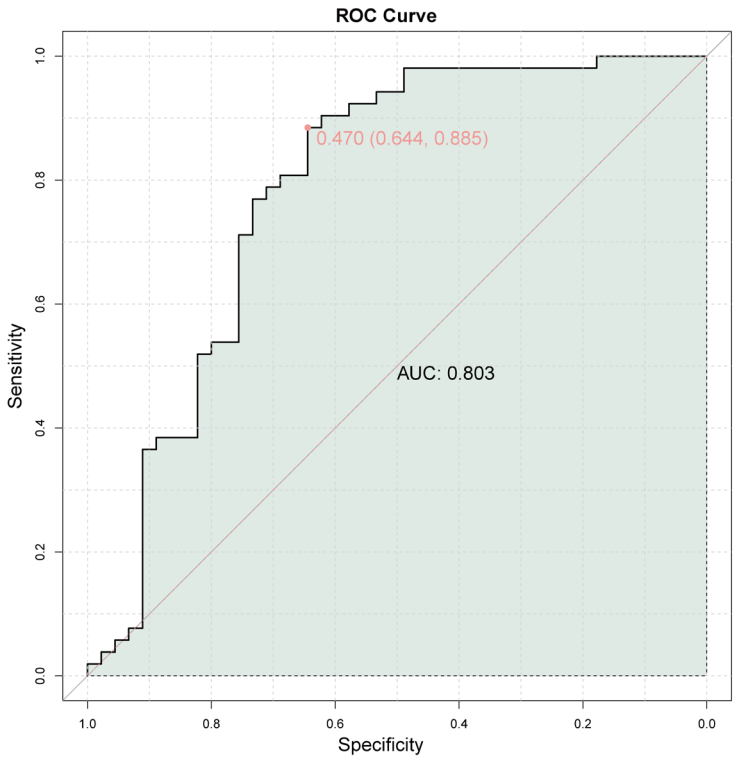

Figure 5. External validation ROC curve. Note: ROC: Receiver Operating Characteristic; AUC: Area Under the Curve.

ferences in prognosis conditions, CRP, IL-6, TNF-α, NLR, CA125, IPS score, and genetic mutations between the two groups are consistent with the findings from the study cohort, supporting the robustness and reliability of the predictive model.

Discussion

This study identified several inflammatory biomarkers, tumor markers, and specific gene mutations that are significantly associated with response to immunotherapy in advanced endometrial cancer. Our findings demonstrate that elevated baseline levels of CRP, IL-6, TNF-α, NLR, CA125, and IPS are independent risk factors for poor response, while BRCA2 and TP53 mutations are independently associated with favorable outcomes. The integration of these parameters into a combined predictive model showed strong discriminative performance.

The significantly increased frequency of mutations in BRCA1, BRCA2, POLE, TP53, and MSH6 among patients with a favorable response provides compelling evidence that deficiencies in DNA damage repair pathways play a crucial role in enhancing tumor immunogenicity and modulating responses to ICIs [14, 15]. Specifically, BRCA1/2 mutations impair homologous recombination repair, leading to the accumulation of double-strand breaks and profound genomic instability [16]. The ensuing presence of cytosolic DNA fragments activates the cyclic GMP-AMP synthase-stimulator of interferon genes pathway, stimulating the production of type I interferons and fostering an immunologically active, inflamed tumor microenvironment that is more susceptible to immune-mediated attack [17]. This mechanism may explain why tumors with homologous recombination repair deficiencies are more amenable to checkpoint blockade, as the inherent immunogenicity might overcome local immunosuppressive mechanisms [18]. Although BRCA1 mutation did not retain independent significance in the multivariate analysis, its initial strong association with response in univariate analysis suggests that it contributes to a permissive immune contexture, possibly in conjunction with other molecular alterations [19].

The retention of BRCA2 and TP53 mutations as independent predictors of favorable response is a particularly noteworthy finding [20]. TP53 mutations, which are common in high-grade and non-endometrioid endometrial cancers, are traditionally associated with aggressive tumor behavior and poor prognosis [21]. The paradoxical association between TP53 mutations and improved immunotherapy response observed in our cohort may be attributed to the role of p53 dysfunction in promoting genomic instability and mutagenesis, thereby generating a diverse repertoire of neoantigens that enhance immune visibility and T-cell recognition [22]. The stronger independent association of BRCA2, compared to BRCA1, with treatment response could reflect differential roles in immune modulation, differences in the spectrum of co-mutations, or tissue-specific biological functions [23]. Further mechanistic studies

are needed to dissect the distinct contributions of these two homologous repair genes to anti-tumor immunity.

POLE and MSH6 mutations further highlight the importance of DNA repair deficiencies [24, 25]. POLE encodes the DNA polymerase epsilon, essential for high-fidelity DNA replication [26]. Mutations in POLE, particularly within its exonuclease domain, drastically increase the ultramutated phenotype-characterized by an exceptionally high TMB [26]. Recent studies [27, 28] have linked POLE-mutant endometrial cancers to a markedly favorable prognosis and impressive responsiveness to immunotherapy, likely due to the abundance of mutation-derived neoantigens. Similarly, MSH6 is a pivotal component of the DNA MMR system, and its inactivation results in MSI [29]. Tumors with MSI-high status, irrespective of tissue origin, have consistently demonstrated heightened sensitivity to PD-1/PD-ligand 1 inhibitors, again implicating TMB and neoantigen load as primary mediators of this effect.

An important layer of complexity is added by the observation that not all mutations exerted equivalent or independent effects in multivariate analyses-BRCA2 and TP53 retained their significance while others did not. This may reflect complex interactions between different elements of the DNA repair machinery, redundancy in their tumor-promoting effects, or differences in their influence over the immunophenotype [30]. For instance, BRCA2 may be more functionally critical in some endometrial tumor subtypes, or perhaps co-mutation with other pathways is necessary to achieve maximal immune responsiveness.

In addition to gene mutations, the role of inflammatory and immune biomarkers emerged prominently. Elevated baseline levels of CRP, IL-6, TNF-α, NLR, CA125, and IPS were all strongly associated with poor immunotherapy response. These findings prompt consideration of how systemic and tumor-driven inflammation modulates immunotherapeutic efficacy. Chronic inflammation, reflected by CRP, IL-6, and TNF-α, is a well-documented enabler of tumor progression and immune evasion [31]. High NLR is indicative of an imbalance between innate, potentially pro-tumor inflammatory responses and adaptive immunity, with neutrophils promoting a suppressive microenvironment that could counteract the benefits of checkpoint blockade [32]. Conversely, low-grade systemic inflammation may be permissive - or even supportive - of anti-tumor immune activation [33]. The elevated CA125 levels in poor responders likely reflect higher tumor burden or more aggressive disease biology, which are factors consistently linked to resistance to immunotherapy across cancer types. CA125, a marker of tumor load and malignant ascites, may indirectly signify an advanced disease state where immunosuppressive networks are more established and difficult to reverse with single-agent immunotherapy.

The IPS emerged as a significant independent predictor in our model. The IPS designed to reflect the cancer immunogenic landscape via multiple components (effector cells, suppressor cells, MHC molecules, immunomodulators), further highlights the multifaceted determinants of immunotherapy outcomes. Tumors with lower IPS may paradoxically mark a subset that is less reliant on immunosuppressive networks or more susceptible to immune engagement upon ICI therapy initiation [34]. It is also possible that in endometrial cancer, the IPS-weighted by immune gene signatures not exclusively predictive of checkpoint response-requires further refinement or tissue-specific calibration to more accurately reflect clinical benefit.

The observation that individual biomarkers exhibited only modest predictive performance underscores the profound complexity and heterogeneity of tumor-immune interactions. Response to immunotherapy is not dictated by a single factor but arises from the dynamic interplay between tumor genetics, the local immune microenvironment, and systemic host factors [35]. This complexity necessitates a multi-analyte approach. The superior accuracy achieved by our combined model, which integrates genetic, inflammatory, and immunological markers, compellingly demonstrates that a multi-dimensional biomarker strategy is essential for generating clinically useful predictions. This approach aligns with the evolving paradigm of precision immuno-oncology, where composite biomarkers are increasingly recognized as necessary to capture the biological nuances of treatment response.

Several limitations should be considered. First, the retrospective design introduces potential

selection bias, though we minimized this through strict inclusion criteria and multivariate adjustment. Second, all patients were from a single institution, which may limit generalizability; however, external validation with an independent cohort strengthened our findings. Third, we focused on a predefined set of genes and biomarkers; other potentially relevant markers, such as additional DNA repair genes or immune checkpoint molecules, were not examined. Finally, the mechanisms underlying the interactions between genetic mutations and inflammatory biomarkers remain speculative and require functional validation.

Future studies should prospectively validate our model in larger, multicentric cohorts. Incorporating additional molecular features, such as TMB, MSI status, and detailed immune cell profiling, could further improve predictive accuracy. Mechanistic investigations are needed to elucidate how specific gene mutations influence the tumor immune microenvironment and inflammatory processes. Additionally, exploring the potential of targeting inflammatory pathways in combination with immunotherapy may provide new therapeutic strategies for resistant cases.

In conclusion, our study provides robust evidences that a model integrating easily measurable inflammatory biomarkers, tumor markers, and specific DNA damage repair gene mutations can effectively predict the responses to immunotherapy in advanced endometrial cancer. These findings reinforce the critical importance of moving beyond single-biomarker approaches and adopting a holistic view that encompasses both tumor-intrinsic genetic factors and host immune and inflammatory status. By validating an accessible and clinically relevant predictive tool, our work supports the future implementation of comprehensive biomarker profiling to guide personalized immunotherapy decisions, ultimately aiming to improve outcomes for patients with this challenging disease.

Disclosure of conflict of interest

None.

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