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ORIGINAL RESEARCH

Nomogram Incorporating Inflammatory Index, Pathology, and Molecular Classification for Predicting Recurrence in Patients with Stage I-III Endometrial Cancer: A Multi-Institutional Study

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Background: This study evaluated the prognostic value of the hemoglobin, albumin, lymphocyte, and platelet (HALP) score for postoperative recurrence in endometrial cancer patients. A nomogram was developed based on clinicopathological parameters, HALP score, and immunohistochemical markers to predict recurrence-free survival (RFS) in patients with stage I–III endometrial cancer.

Methods: This retrospective study included 1,083 patients who underwent hysterectomy at the First Affiliated Hospital of Chongqing Medical University from January 2013 to January 2021. Independent risk factors for RFS were identified using univariate and multivariate Cox regression analyses, and a nomogram was established. External validation was performed with data from Zhujiang Hospital of Southern Medical University and Women and Children's Hospital of Chongqing Medical University (n = 677).

Results: Among the entire cohort, 241 cases (13.7%) of endometrial cancer experienced recurrence post-hysterectomy. The median RFS time was 47.0 (range: 6.0–91.0) months. Eleven independent prognostic factors were identified, including age, FIGO staging, histologic type, myometrial invasion, lymphovascular space invasion, Ca125, Ki-67 expression, ER expression, molecular classification, adjuvant therapy, and HALP score, and then a nomogram for predicting recurrence of endometrial cancer was established. The nomogram demonstrated improved predictive accuracy, categorizing patients into high- and low-risk groups. High-risk patients receiving adjuvant treatment had better outcomes than those who did not.

Conclusion: We developed and validated a nomogram to predict recurrence in endometrial cancer patients. Integrating the HALP score can help clinicians identify high-risk patients and tailor personalized treatment strategies.

Keywords: endometrial cancer, prognosis, nomogram, HALP scores, adjuvant therapy, molecular classification

Introduction

Endometrial carcinoma is the most prevalent gynecologic malignancy, with an estimated incidence rate of 15.6–19.1 per 100,000 in North America and Western Europe.[1] The prevalence of endometrial cancer in China has significantly increased over the last decade, which can be attributed to lifestyle changes and rising rates of obesity.[2] Most patients diagnosed with endometrial cancer are identified at an early stage. Following surgical intervention, these patients often achieve a favorable prognosis, which contributes to a 5-year survival rate of approximately 80%. However, recurrence and metastasis remain

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significant factors that adversely affect the prognosis associated with this condition.[3] Therefore, it is crucial to identify and determine the factors that influence survival in order to alleviate the rising burden of the disease.[2]

In the past, the prognosis of endometrial cancer was usually predicted based on a complete surgical staging system and traditional clinicopathological parameters. Nevertheless, patients with matching clinical staging and equivalent treatment regimens frequently demonstrate variations in survival rates, suggesting that a surgical staging system reliant on anatomical factors may not adequately evaluate the prognosis of endometrial cancer. In recent years, the Cancer Genome Atlas (TCGA) research project has proposed a molecular classification for endometrial cancer, categorizing it into four subtypes based on multi-omics features and their association with prognosis: DNA polymerase epsilon catalytic subunit (*POLE*) ultra-mutated, microsatellite instability (MSI), copy-number low (CN-L), and copy-number high (CN-H).[4] Subsequent research has consistently verified the prognostic significance of this novel molecular classification, leading to its incorporation into the updated FIGO staging guidelines. Therefore, further exploration of prognostic factors associated with prognosis in endometrial cancer is crucial for supplementing and enhancing the existing prognostic assessment strategy. This endeavor will provide valuable insights for clinical treatment and potentially even immunotherapy, improving patient outcomes.

Extensive studies have suggested that the local immune activity and systemic inflammatory processes play significant roles in tumor growth and clinical outcomes.[5–7] In clinical practice, the nutritional, immune, and inflammatory status of patients can be easily detected and accessed through preoperative routine blood tests. Recent oncological studies have increasingly utilized the integrated HALP score (combining hemoglobin, albumin, lymphocyte, and platelet parameters) as a robust predictor of clinical outcomes, particularly in urological (bladder carcinoma)[8] and gastrointestinal malignancies (gastric[9] and colorectal carcinoma).[10,11] However, there are few studies reporting the potential prognostic utility of the HALP score in endometrial cancer, and the evidence supporting its clinical translation is relatively limited.

The study investigated the relationship between the pre-treatment HALP score and clinical outcomes in a retrospective cohort of endometrial cancer patients. Additionally, we aimed to integrate clinical-pathological parameters, the HALP score, and molecular markers to develop a predictive model for a comprehensive assessment of patient prognosis and to guide clinical practice.

Materials and Methods

Patient Selection

Patient records of individuals with stage I to III endometrial carcinoma who received surgical treatment at various Chinese hospitals during the period of 2014–2021 were examined. The dataset comprised 1,083 cases for model development from the First Affiliated Hospital of Chongqing Medical University (FAHCQMU) and 677 cases for independent validation from Zhujiang Hospital, Southern Medical University (ZJHSMU) and Women and Children's Hospital of Chongqing Medical University (WCHCQMU).

The study established the following exclusion criteria: i) individuals not undergoing standard surgical procedures; ii) inadequate lymph node examination; iii) previous neoadjuvant therapy administration; iv) existing inflammatory/immune disorders;[12] v) incomplete medical records; vi) follow-up discontinuation; vii) coexisting malignant neoplasms; and viii) unavailable preoperative HALP scores. Figure 1 provides a schematic overview of the study design.

Treatment

The entire cohort underwent comprehensive surgical staging procedures and pathological classification. Then, therapeutic recommendations, including observation or various postoperative adjuvant therapies, were made according to guidelines and risk factor evaluations. Radiotherapy primarily involved two regimens: vaginal brachytherapy and pelvic external beam radiotherapy. Regarding vaginal brachytherapy, patients received a cumulative radiation dose between 22.0 and 24.0 Gy, administered in four treatment sessions at 5.5–6.0 Gy per fraction. Pelvic external beam radiotherapy involved a total dosage of 45.0–50.0 Gy, divided into 25 fractions with daily doses of 1.8–2.0 Gy. Both treatment modalities were completed within a 12-week postoperative period. Patients received the TP regimen (platinum-paclitaxel combination chemotherapy, the standard first-line treatment) in 3-week cycles, with treatment duration spanning 6–8 cycles.[13–15] The

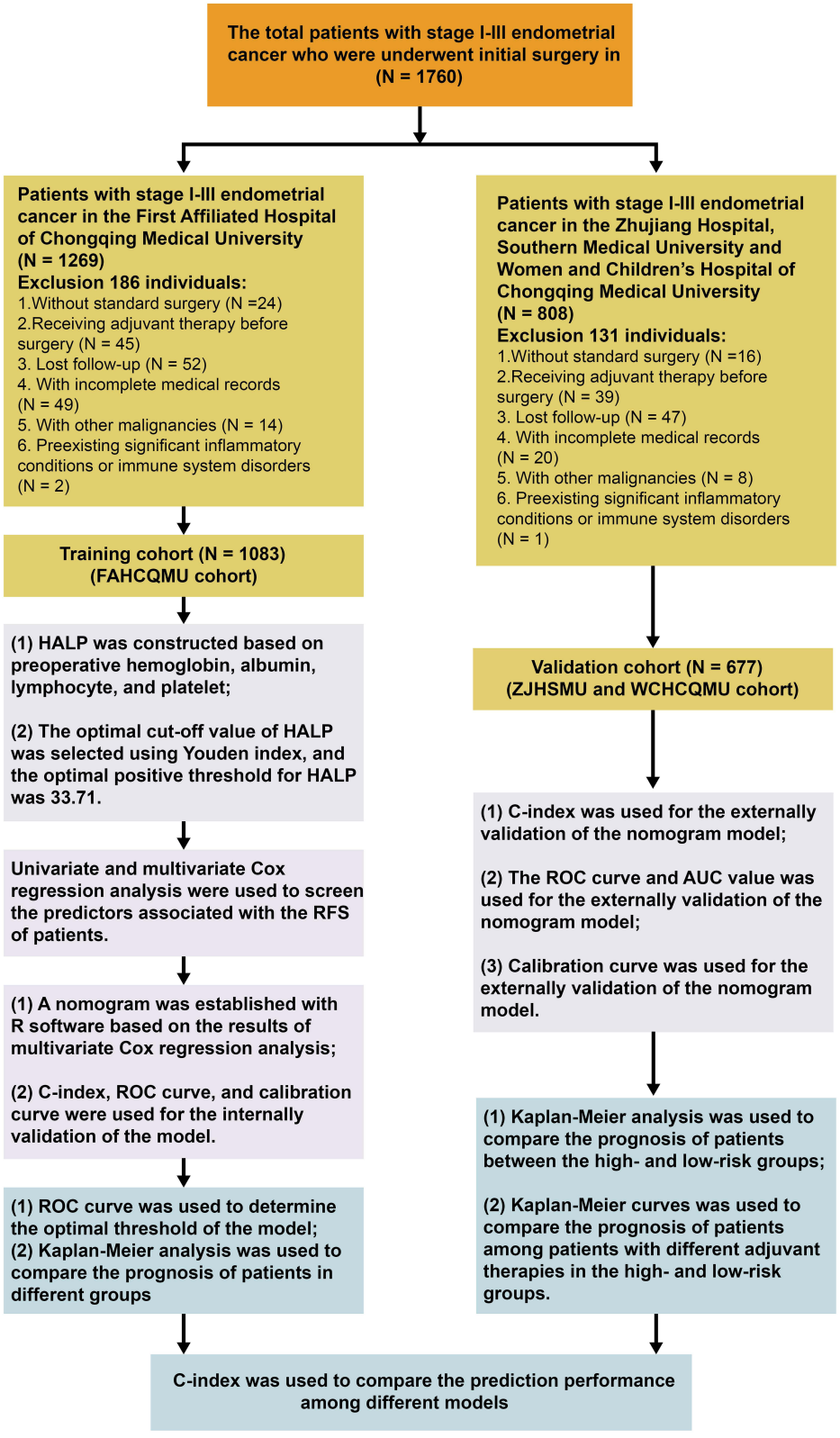

Figure 1 Flowchart providing a comprehensive overview of the inclusion and exclusion criteria for the study cohorts.

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treatment at other medical centers was standardized according to the treatment plan of the First Affiliated Hospital of Chongqing Medical University.[13]

Variable and Outcomes

Clinicopathological data and surgical details were meticulously gathered by trained medical assistants, and medical records were maintained using standardized data collection forms. Specifically, this information included age at diagnosis, body mass index (BMI), histological type, cervical stromal invasion, depth of myometrial invasion, lympho-vascular space invasion (LVSI), International Federation of Gynecology and Obstetrics (FIGO) stage, molecular markers (Ca125 level, Ki-67, ER, PR, MMR protein, and P53), adjuvant therapy, and HALP score. Routine blood results were collected within one week prior to the operation, and the HALP score was calculated from the routine blood test results for hemoglobin, albumin, lymphocytes, and platelets, using the following formula: (hemoglobin [g/L] x albumin [g/L] x lymphocytes [/L]) /platelets [/L]. The optimal cut-off value for HALP score was determined using the Youden index.[16] With the established positive threshold for HALP set at 33.71, patients were categorized into high-HALP and low-HALP groups (Figure 2). This classification aligns with the findings from our previous small-sample, single-center study.[17]

Patients received follow-up assessments at 3-month intervals during the initial 2 years, transitioning to 6-month intervals for years 3–5, and subsequently annual evaluations. Recurrence was detected through physical examinations and/or imaging modalities, with histological confirmation obtained. Recurrence-free survival (RFS) was defined as the interval from the initial surgery to the first locoregional or distant relapse. The last follow-up data for this study was July 25, 2023.

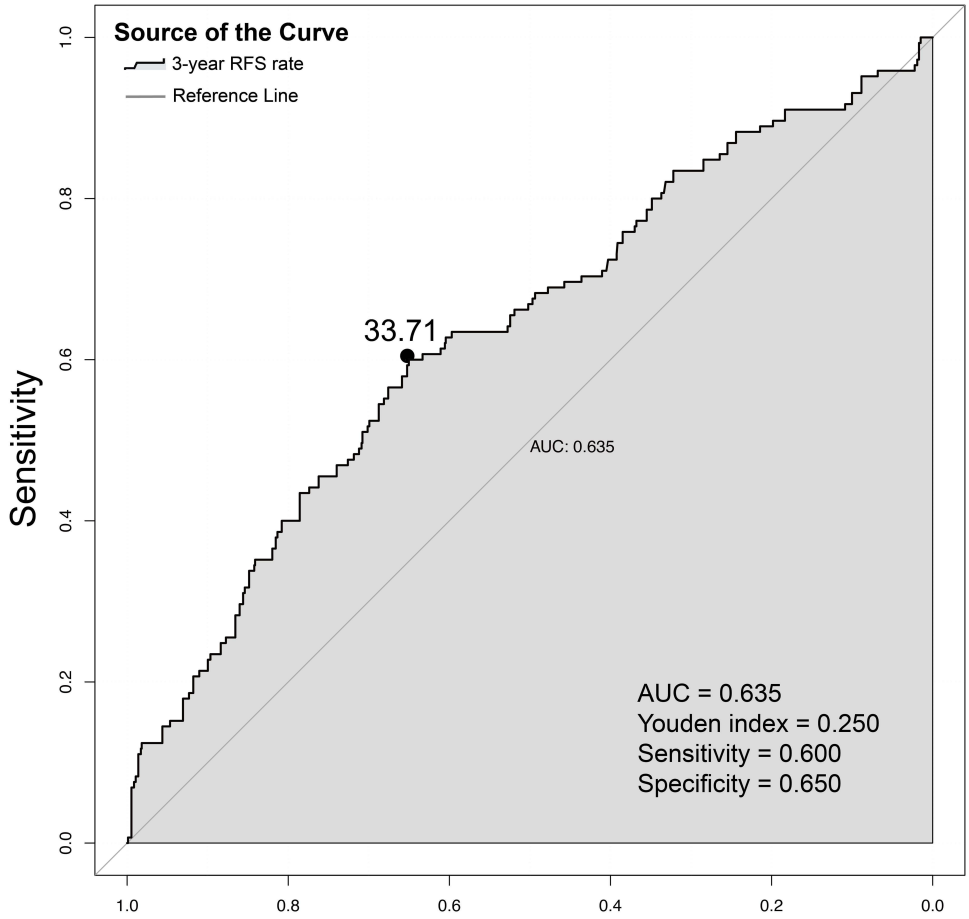

Figure 2 The ROC curves of HALP score for predicting the recurrence of endometrial cancer. The black dot represents the optimal cutoff value (value = 33.71) of the corresponding HALP scores for predicting endometrial cancer recurrence.

Histology and Immunohistochemistry

The study performed immunohistochemical (IHC) analysis on formalin-fixed, paraffin-embedded tissue samples, with all pathological specimens being examined by qualified pathologists. The results of P53 IHC was classified as normal, defined as 1–80% of cancer cell nuclei exhibiting positive staining, or abnormal, characterized by either the absence of nuclear staining in cancer cells or uniform and intense nuclear staining in at least 80% of cancer cell nuclei.[18] According to our previous study, Ki-67 were categorized as high Ki-67 expression (the proportion of Ki-67 positive cells ≥ 40%) and low Ki-67 expression (positive cells < 40%).[19,20] Simultaneously, the proportion of ER and PR positive cells ≤ 5% was defined as negative expression, while > 5% was defined as positive.[19]

Statistical Analysis

From 2013 to 2021, we collected data from endometrial cancer patients at three medical centers and assigned them into training and external validation cohorts. Categorical data were presented as frequencies and percentages, with statistical comparison analyzed using the $\chi 2$ or Fisher's exact test. Continuous variables were presented as means with standard deviations, and compared using independent samples *t* test. All candidate predictors underwent multivariate Cox proportional hazards modeling, with factors demonstrating significance at the 0.05 threshold classified as independent prognostic indicators. Survival distributions were visualized through Kaplan-Meier plots, and intergroup survival differences were evaluated via log-rank test. Statistical significance was defined as *P*-values <0.05. Data processing and analysis were conducted using SPSS Statistics (v24.0) alongside R software (v3.6.1).[3]

Results

Patient Characteristics

In this study, a total of 1760 patients with endometrial cancer were enrolled from three large medical institutes in China, adhering to the established exclusion criteria. The clinicopathological parameters, treatment details, and follow-up data were summarized in Table 1, while all routine blood results were collected one week before the surgery (Supplementary Table 1). In the entire study cohort, the average age of patients was 53.86 ± 9.50 years, with the majority being at FIGO stage I (1221, 69.4%), exhibiting superficial myometrial invasion (1228, 69.8%), negative LVSI (1298, 73.7%), and predominantly histological type I (1265, 71.9%). In terms of molecular markers, the majority of patients showed serum Ca125 levels ≤ 35 U/mL (1319, 74.9%), Ki-67 low expression (1032, 58.6%), ER positive expression (1437, 81.6%), PR positive expression (1371, 77.9%), dMMR status (883, 50.2%), and high-HALP scores (1085, 61.6%).

Table 1 Demographic and Clinical Characteristics of Patients with Endometrial Cancer

Characteristic	Whole Population [Cases (%)]	Training Cohort [Cases (%)]	Validation Cohort [Cases (%)]	*P* Value
Total	1760	1083	677	
Age (years)	53.86 ± 9.50	53.81 ± 9.47	53.94 ± 9.54	0.791
BMI (kg/m^2)	24.53 ± 3.62	24.56 ± 3.69	24.50 ± 3.51	0.734
FIGO staging				0.422
I	1221 (69.4)	760 (70.1)	461 (68.0)	
II	172 (9.8)	108 (10.0)	64 (9.5)	
III	367 (20.8)	215 (19.9)	152 (22.5)	
Histological type				0.695
Type I	1265 (71.9)	782 (72.2)	483 (71.3)	
Type II	495 (28.1)	301 (27.8)	194 (28.7)	
Myometrial invasion				0.720
< 1/2	1228 (69.8)	759 (70.1)	469 (69.3)	
≥ 1/2	532 (30.2)	324 (29.9)	208 (30.7)	

(*Continued*)

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Table 1 (Continued).

Characteristic	Whole Population [Cases (%)]	Training Cohort [Cases (%)]	Validation Cohort [Cases (%)]	*P* Value
Cervical stromal invasion				0.655
No	1439 (81.8)	889 (82.1)	550 (81.2)	
Yes	321 (18.2)	194 (17.9)	127 (18.8)	
LVSI				0.356
Negative	1298 (73.7)	807 (74.5)	491 (72.5)	
Positive	462 (26.3)	276 (25.5)	186 (27.5)	
Serum Ca125 (U/mL)				0.853
≤ 35	1319 (74.9)	810 (74.8)	509 (75.2)	
> 35	441 (25.1)	273 (25.2)	168 (24.8)	
Ki-67 expression				0.763
Low	1032 (58.6)	632 (58.4)	400 (59.1)	
High	728 (41.4)	451 (41.6)	277 (40.9)	
ER expression				0.326
Positive	1437 (81.6)	892 (82.4)	545 (81.6)	
Negative	323 (18.4)	191 (17.6)	132 (18.4)	
PR expression				0.269
Positive	1371 (77.9)	853 (78.8)	518 (76.5)	
Negative	389 (22.1)	230 (21.2)	159 (23.5)	
Molecular classification				0.458
dMMR	883 (50.2)	531 (49.0)	352 (52.0)	
P53abn	485 (27.5)	303 (28.0)	182 (26.9)	
pMMR and P53wt	392 (22.3)	249 (23.0)	143 (21.1)	
HALP score				0.964
Mean (±SD)	41.90 ± 21.71	41.92 ± 21.85	41.87 ± 21.49	
≥33.71	1085 (61.6)	666 (61.5)	419 (61.9)	0.868
<33.71	675 (38.4)	417 (38.5)	258 (38.1)	
Adjuvant treatment				0.722
Follow-up	659 (37.4)	412 (38.1)	247 (36.5)	
Radiotherapy only	557 (31.7)	347 (32.0)	210 (31.0)	
Chemotherapy only	58 (3.3)	34 (3.1)	24 (3.5)	
Chemoradiotherapy	486 (27.6)	290 (26.8)	196 (29.0)	
Recurrence				0.638
No	1519 (86.3)	938 (86.6)	581 (85.8)	
Yes	241 (13.7)	145 (13.4)	96 (14.2)	
RFS time (months)				0.536
Mean (±SD)	49.63 ± 19.18	49.85 ± 19.15	49.27 ± 19.23	
Median (range)	47.0 (6.0–91.0)	47.0 (6.0–91.0)	47.0 (6.0–91.0)	
Follow-up (months)				0.634
Mean (±SD)	52.16 ± 17.47	52.31 ± 17.42	51.91 ± 17.56	
Median (range)	49.0 (7.0–91.0)	49.0 (7.0–91.0)	48.0 (8.0–91.0)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; dMMR, mismatch repair deficiency; pMMR, mismatch repair proficiency; P53abn, P53 abnormality; P53wt, P53 wild-type; SD, standard deviation; RFS, recurrence-free survival; HALP, hemoglobin, albumin, lymphocyte, and platelet.

In terms of adjuvant treatment, a total of 1101 patients underwent postoperative adjuvant therapy, with 557 (31.7%) receiving radiotherapy, 58 (3.3%) receiving chemotherapy, and 486 (27.6%) receiving chemoradiotherapy. The patients were followed for a mean duration of 52.16 ± 17.47 months. During the observation period, 13.7% of patients (n=241) exhibited disease recurrence, demonstrating a median RFS of 47 months (6–91 months range). The baseline demographic features showed comparable distributions between training and external validation sets according to chi-square testing.

Independent Prognostic Factors Associated with Recurrence of Endometrial Cancer

Within the training set, the parameters of clinicopathologic features, preoperative HALP score, and molecular markers were included in univariate and multivariate Cox regression analysis results for prediction of RFS after hysterectomy. After stepwise backward variable selection, only the following variables were identified as independent prognostic factors for the RFS of patients: age, histologic type, FIGO stage, myometrial invasion, LVSI status, Ca125, Ki-67 expression, ER expression, molecular classification, adjuvant therapy, and HALP score (All $P < 0.05$, Table 2). Among these factors, age ≥ 60 years [hazard ratio (HR) 1.699, 95% confidence interval (CI) 1.194–2.418], FIGO stage III (HR 2.109, 95% CI 1.317–3.377), histological type II (HR 1.970, 95% CI 1.270–3.055), deep infiltration of the myometrium (HR 1.676, 95% CI 1.149–2.446), positive LVSI (HR 1.736, 95% CI 1.173–2.571), Ca125 >35 U/mL (HR 1.481, 95% CI 1.033–2.124), Ki-67 high expression (HR 1.566, 95% CI 1.082–2.267), ER positive expression (HR 1.781, 95% CI 1.085–2.923), P53abn (HR 2.747, 95% CI 1.801–4.188), and low-HALP score (HR 1.988, 95% CI 1.401–2.821) were the independent risk factors for RFS; whereas receiving adjuvant therapy (HR 0.567, 95% CI 0.361–0.892) was the independent protective factor of RFS.

Development and Validation of Nomogram

A nomogram incorporating these independent risk factors was established based on multivariate Cox regression analysis (Figure 3). The nomogram provides a convenient and accurate method for predicting the RFS of patients, as demonstrated in the following example: a 62-year-old female patient (48 pts), clinically diagnosed FIGO stage II (17 pts), with endometrioid adenocarcinoma (histological type I, 0 pts), deep myometrial invasion (56 pts), positive LVSI (59 pts), serum Ca125 level of 12.2 U/mL (0 pts), preoperative HALP score of 42.1 (0 pts), immunohistochemistry showed Ki-67 < 40% (0 pts), ER > 5% (0 pts), abnormal P53 expression (100 pts), and received adjuvant therapy postoperatively (0 pts). The total score of 280 points was associated with RFS rates of 90% at 1 year and 80% at 3 years(refer to Supplementary Table 2 for individual nomogram scores).

Within the training cohort, the concordance index of the endometrial cancer prediction nomogram was 0.856 [95% CI, 0.831–0.881]. In the external validation cohort, the model achieved a concordance index of 0.853 (95% CI, 0.820–0.886). The time-dependent ROC curves demonstrated that the nomogram model could effectively differentiate the prognoses of endometrial

Table 2 Univariate and Multivariate Analysis of Factors Predicting Endometrial Cancer Recurrence in the Training Cohort

Variables	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Age (≥60 yrs vs < 60 yrs)	2.037	1.460–2.843	<0.001	1.699	1.194–2.418	0.003
FIGO stage						
I	Reference		<0.001	Reference		0.005
II	2.273	1.273–4.058	0.006	1.304	0.631–2.694	0.474
III	7.518	5.262–10.741	<0.001	2.109	1.317–3.377	0.002
Histological type (Type I vs Type II)	5.932	4.203–8.371	<0.001	1.970	1.270–3.055	0.002
Myometrial invasion (≥1/2 vs <1/2)	3.659	2.630–5.089	<0.001	1.676	1.149–2.446	0.007
Cervical stromal invasion (Yes vs No)	2.885	2.054–4.051	<0.001	1.329	0.854–2.068	0.208
LVSI (Positive vs Negative)	4.374	3.148–6.077	<0.001	1.736	1.173–2.571	0.006
Serum Ca125 (>35 U/mL vs ≤ 35 U/mL)	2.716	1.958–3.766	<0.001	1.481	1.033–2.124	0.033
Ki-67 expression (High vs Low)	2.779	1.976–3.909	<0.001	1.566	1.082–2.267	0.018
ER expression (Negative vs Positive)	5.597	4.039–7.755	<0.001	1.781	1.085–2.923	0.022
PR expression (Negative vs Positive)	4.522	3.264–6.264	<0.001	1.036	0.628–1.709	0.889
Molecular classification						
dMMR	Reference		<0.001	Reference		<0.001
P53abn	2.218	1.419–3.465	<0.001	1.407	0.891–2.222	0.143
pMMR and P53wt	4.532	3.011–6.821	<0.001	2.747	1.801–4.188	<0.001
Adjuvant treatment (No vs Yes)	2.183	1.481–3.219	<0.001	0.567	0.361–0.892	0.014
HALP score (<33.71 vs ≥33.71)	2.552	1.830–3.557	<0.001	1.988	1.401–2.821	<0.001

Abbreviations: CI, confidence interval; dMMR, mismatch repair deficiency; pMMR, mismatch repair proficiency; P53abn, P53 abnormality; P53wt, P53 wild-type.

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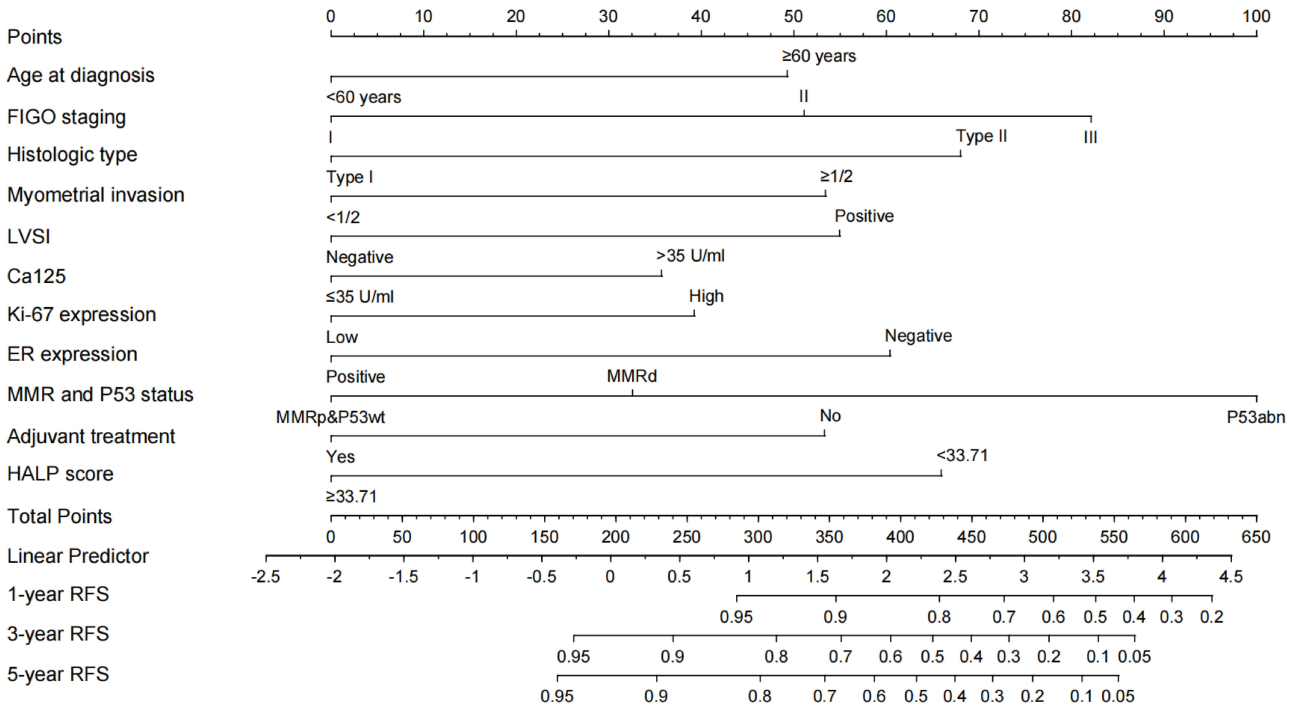

Figure 3 Nomogram model for predicting the 1-, 3-, and 5-year RFS rates of endometrial cancer patients.

cancer patients undergoing hysterectomy over time in both the training and validation cohorts (Figure 4A and B). The calibration curves of the model demonstrated that the predicted 1-, 3- and 5-year RFS rates closely matched the actual survival rates within a margin of error of 10% (Figure 4C–H).

Prognostic Score for Risk Stratification and Therapeutic Decision-Making

Based on the nomogram scores, patients with endometrial cancer in the training cohort were classified into two groups: a low-risk group (3-year RFS rate > 0.886, n = 798 cases) and a high-risk group (3-year RFS rate ≤ 0.886, n = 285 cases) (Supplementary Figure 1). The survival curves demonstrated that high-risk patients experienced significantly poorer clinical outcomes (OS and RFS) compared to those in the low-risk group (All $P < 0.001$, Figure 5). Interestingly, among high-risk patients, those who received adjuvant therapy exhibited considerably more favorable prognoses than those who did not receive therapeutic intervention (All $P < 0.05$, Figure 6). The analysis of low-risk cases showed that adjuvant therapy did not provide any significant advantage in terms of RFS or OS compared to patients who did not receive adjuvant therapy (Supplementary Figure 2). Consistent with the findings in the training cohort, the results were replicated in the external validation cohort, and the detailed survival rates for patients in the high- and low-risk groups can be found in Supplementary Table 3.

Discussion

The immune inflammatory response is mediated by circulating immune inflammatory cells, which can induce drug resistance in malignant cells, modify the tumor microenvironment, and play an essential role in the occurrence and progression of cancer.[21,22] In recent years, various immune-nutritional and inflammatory indices have been proposed as potential prognostic markers for endometrial cancer, including the prognostic nutritional index (PNI), platelet-to-lymphocyte ratio (PLR), Glasgow prognostic score (GPS), inflammation-immunity-nutrition score (IINS), among others.[23] Accumulating evidence proves that these peripheral blood inflammatory markers can not only predict the prognosis of various malignancies but also evaluate the risk of cancer recurrence and guide clinical practice.

Since Chen et al[24] described a novel nutrition-immune-inflammation-based index known as HALP in 2015, which demonstrated significant prognostic value in patients with gastric cancer. In this study, we found that lower HALP scores were closely associated with higher recurrence probabilities and worse outcomes in endometrial cancer. Similar findings have

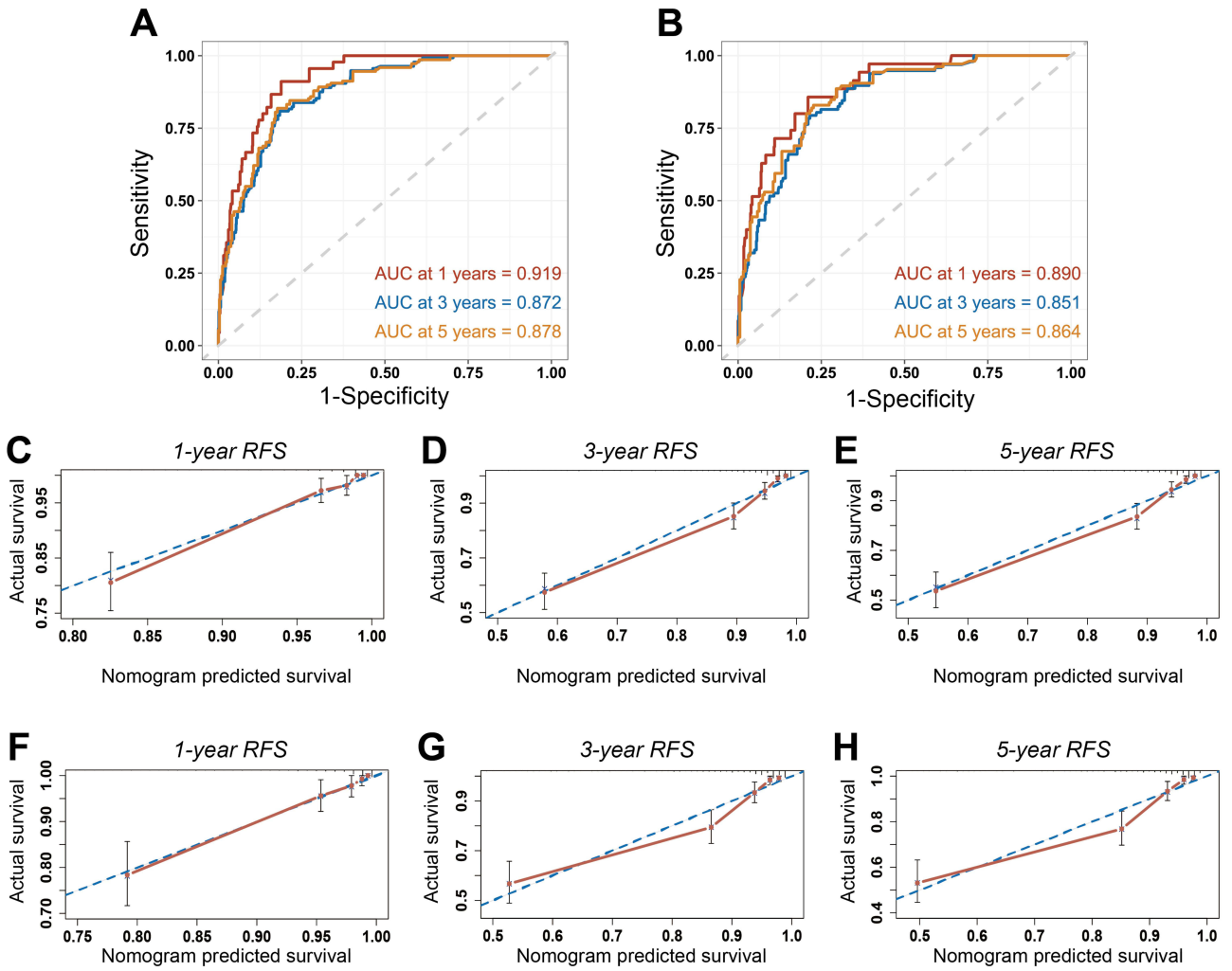

Figure 4 The ROC curves with corresponding AUC values demonstrating the predictive performance of the nomogram in both training (**A**) and validation sets (**B**); The calibration plots evaluating the nomogram's accuracy across the training (**C**–**E**) and validation sets (**F**–**H**).

been reported in other solid tumors, including lung carcinoma and esophageal carcinoma. However, the optimal cut-off for HALP differs among various malignancies, with 36.87 for lung cancer[25] and 23.1 for esophageal cancer.[26] We determined and adopted the optimal cutoff for HALP in endometrial cancer patients to be 33.71. Utilizing this threshold, HALP scores effectively identified high-risk patient subgroups and served as a predictive indicator for postoperative RFS in endometrial cancer. Even after controlling for the concomitant effects of known clinical high-risk factors, HALP remained an independent predictor of RFS for this disease. The predictive capacity of HALP regarding endometrial cancer recurrence, however, remains substantially constrained. Therefore, we integrated HALP with other clinicopathological factors and molecular classifications to develop a nomogram that intuitively quantifies and displays the individualized nutritional-immune-inflammatory status of endometrial cancer patients. Based on three independent cohorts, we conducted external validation of the predictive accuracy of the model. The predictive performance was found to be moderately strong, as evidenced by C-index and ROC curve analyses. Through this multi-factor predictive model, gynecologic oncologists can accurately predict the prognosis for each individual. By calculating the risk scores based on various risk factors, clinicians can optimize prognostic management and clinical decision-making for endometrial cancer patients, thereby enabling a more tailored and comprehensive treatment plan while minimizing the risk of recurrence. Additionally, this tool empowers patients to gain a clearer understanding of their health status, fostering active participation in their treatment and recovery processes, ultimately improving their quality of life.

Presently, supplementary treatments administered after surgery play a pivotal role in managing localized cancer recurrence in patients with endometrial malignancies.[23] According to the NCCN clinical practice guidelines, postoperative adjuvant

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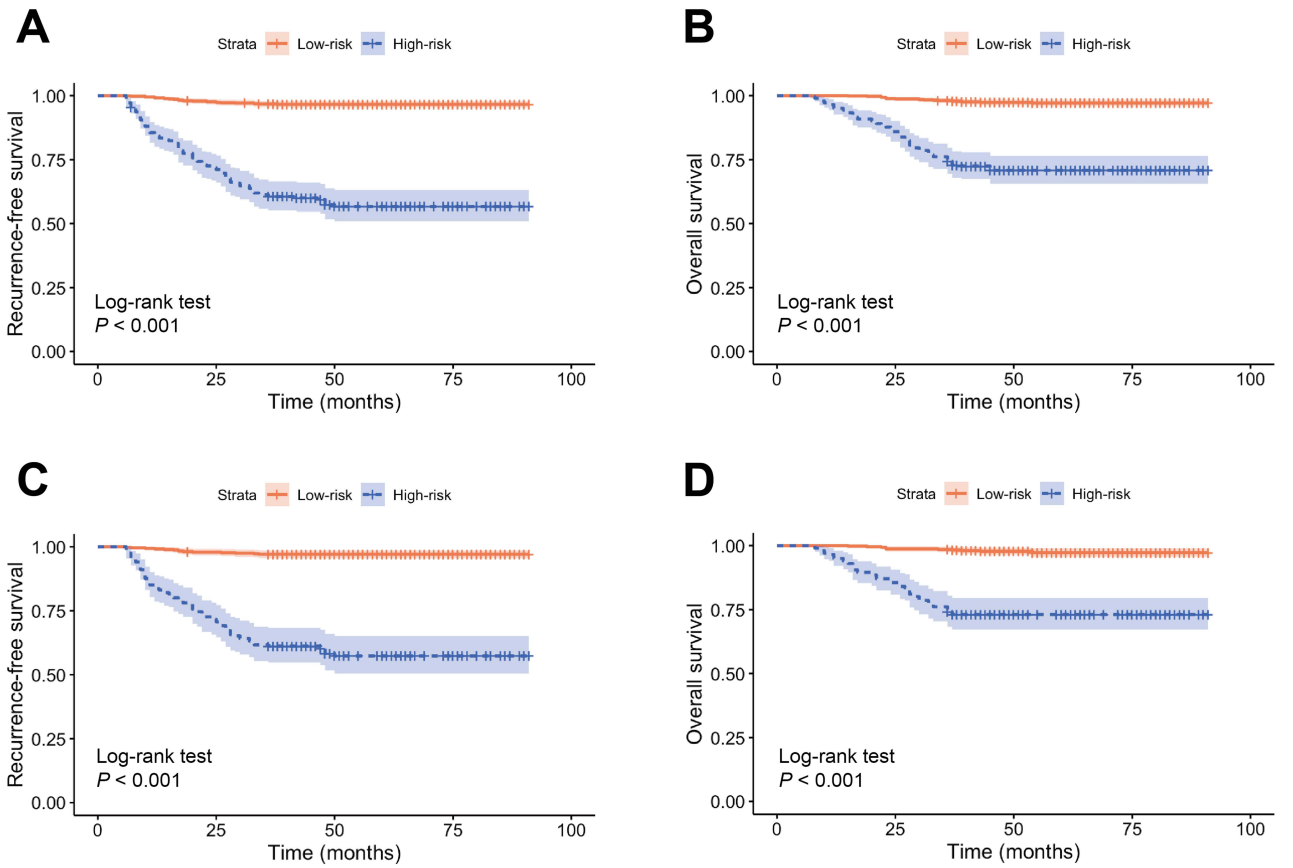

Figure 5 Kaplan-Meier survival analysis comparing high- and low-risk patients in training and validation cohorts. (**A**) RFS and (**B**) OS curves of high and low-risk groups in the training set; (**C**) RFS and (**D**) OS curves of high and low-risk groups in the validation set.

radiotherapy (either alone or in combination with chemotherapy) is essential for high-risk endometrial cancer patients presenting with any of the following indicators: advanced age (> 60 years), poorly differentiated tumors, non-endometrioid histology, extensive myometrial or cervical invasion, or advanced FIGO stage (stage III–IV). Furthermore, our model categorizes patients into high- and low-risk groups, revealing that the survival probabilities for high-risk patients are significantly lower than those for low-risk patients. This underscores the importance of focusing on high-risk patients identified by predictive models, advocating for more aggressive adjuvant treatment and close surveillance for this population. These recommendations are supported by large-sample, multicenter clinical evidence, indicating that such interventions significantly improve outcomes for high-risk patients by reducing the likelihood of local recurrence. Notably, we observed that some patients did not receive postoperative adjuvant therapy in accordance with the guidelines due to the absence of overt high-risk clinical and pathological factors, despite their molecular markers and HALP indicating poor prognosis. For instance, one patient exhibited clinical and pathological features consistent with low risk, including age < 60 years (0 pts), FIGO stage I (0 pts), histologic type I (0 pts), myometrial invasion < 50% (0 pts), and negative LVSI (0 pts). Additionally, this patient had a Ca125 level of 48.2 U/mL (39 pts), Ki-67 expression of 60% (38 pts), ER expression of < 5% (66 pts), abnormal P53 expression (100 pts) and a HALP score of less than 19.11 (64 pts). Ultimately, the 3-year RFS probability of this patient was calculated to be 0.78 categorizing them as high risk based on the model's cut-off value of 0.866. This highlights the need to consider not only the clinicopathological characteristics of endometrial cancer but also the patients' nutritional, immune, and inflammatory status, along with molecular classifications.

In recent years, many prediction models and molecular score systems have been proposed and utilized. However, the high cost of detection and the complexity of detection strategies make it difficult to widely implement in many regions. The nomogram model established in this study is based on clinically available variables and preoperative serum biomarkers, facilitating its straightforward utilization by clinicians without additional medical expenses. Furthermore, the nomogram model was based on a large population-based cohort, which enhances its generalizability. Additionally, the nomogram model

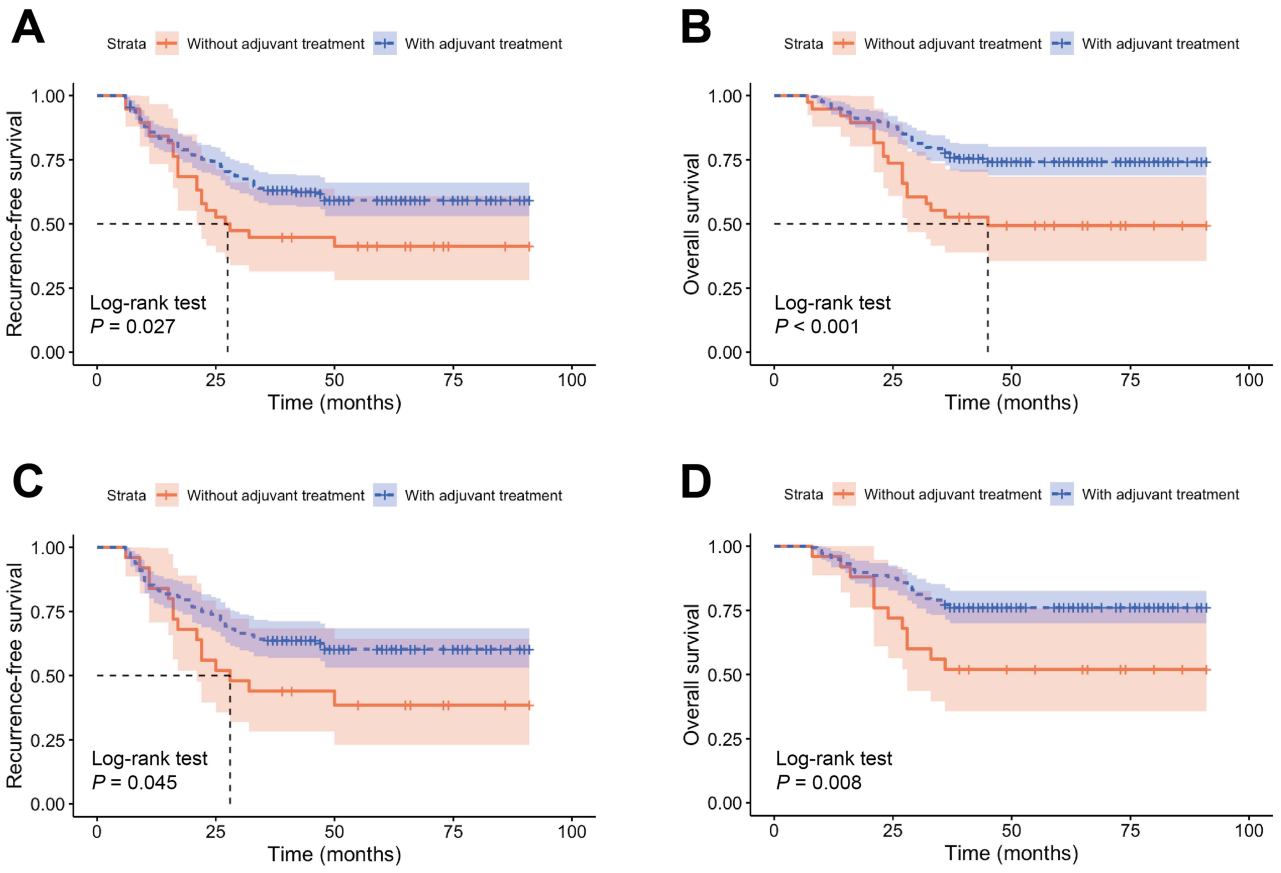

Figure 6 Comparison of RFS and OS in high-risk endometrial cancer patients with or without adjuvant treatment post-operatively. (**A**) Training cohort of the RFS ($P_{\text{adjuvant treatment vs untreated}}$ = 0.027); (**B**) Training cohort of the OS ($P_{\text{adjuvant treatment vs untreated}}$ < 0.001); (**C**) External validation cohort of the RFS ($P_{\text{adjuvant treatment vs untreated}}$ = 0.045); (**D**) External validation cohort of the OS ($P_{\text{adjuvant treatment vs untreated}}$ = 0.008).

established in this study was compared with previous risk stratification systems, and the results demonstrated that our model is more flexible, easier to use, and exhibits higher predictive accuracy and discrimination (Table 3).

Several limitations of the study should also be discussed. Firstly, this study is retrospective and further validation is needed in multicenter prospective studies. Secondly, due to the retrospective nature of data collection and the extensive data collection

Table 3 The Predictive Performance of Different Risk Stratification for Predicting Endometrial Cancer Recurrence

Risk Stratification	Key Predictors of the Prediction Model	C-Index (95% CI)	
		Training Set	Validation Set
Model A[27]	A nomogram including age, surgical staging, histological grade, LVSI, FIGO staging.	0.799 (0.764–0.834)	0.781 (0.744–0.818)
Model B[17]	An inflammation scoring system based on HALP scores.	0.647 (0.600–0.694)	0.615 (0.576–0.654)
Model C[13]	A nomogram model including histological type, FIGO stage, myometrial invasion, LVSI, P53 expression, and MMR status.	0.828 (0.797–0.859)	0.810 (0.773–0.847)
Our model	A nomogram including age, histological type, FIGO stage, myometrial invasion, LVSI, serum Ca125, Ki-67 expression, ER expression, MMR & P53 expression, HALP score, adjuvant treatment.	0.856 (0.831–0.881)	0.853 (0.820–0.886)

Notes: Comparing predictive performance among different models using the C-index.
Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphatic vessel space invasion; PLR, platelet/lymphocyte ratio; SIRI, systemic inflammation response index; HALP, hemoglobin, albumin, lymphocyte, and platelet.

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period, many patients did not undergo testing for *POLE* mutation status, resulting in an incomplete molecular classification when integrating the established model in the present study. Some patients harboring both *POLE* mutations and *P53* abnormalities may be categorized by the model as high-risk, leading to an overestimation of recurrence risk for these patients. However, in reality, the proportion of patients with *POLE* mutations in endometrial cancer is low (range from 5 to 8%), and the proportion of patients with multiple molecular subtypes is quite lower, estimated at around 3–5%.[28,29] Consequently, the model only slightly overestimates the recurrence risk, with most endometrial cancer patients being accurately assessed. The high cost of NGS technology restricts the widespread implementation of molecular subtyping. Therefore, this model can serve as a supplementary tool to assist in evaluating prognosis and formulating treatment strategies. Future studies could evaluate whether rare patients harboring *POLE* mutations are accurately predicted by this model and identify the most appropriate model able to take this aspect into account.

Conclusion

In this large multi-center study, the pre-treatment HALP score was identified as an independent prognostic biomarker for endometrial cancer. We developed an integrated model that combines clinicopathological, nutritional, immunological, and molecular factors to predict the risk of recurrence, thereby enabling personalized postoperative risk stratification. High-risk patients demonstrated significantly higher rates of recurrence and mortality, highlighting the potential benefits of aggressive adjuvant therapy.

Data Sharing Statement

The datasets employed in this investigation are accessible from the corresponding author upon justified request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Chongqing Medical University (IRB No. 2021-676), Zhujiang Hospital, Southern Medical University (IRB No. 2024-KY-406-02), and Women and Children's Hospital of Chongqing Medical University (IRB No. 2023-02). All patients provided informed consent prior to treatment initiation and agreed to the publication of their data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared no conflicts of interest in this study.

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