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ORIGINAL RESEARCH

Predicting the Recurrence of Operable Cervical Cancer Patients Based on Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score and Classical Clinicopathological Parameters

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Objective: The purpose of this study was to evaluate the prognostic value of hemoglobin, albumin, lymphocyte, and platelet (HALP) score in patients with operable cervical cancer, and on this basis, combined with classical clinicopathological parameters to predict the recurrence of patients.

Methods: A total of 1580 patients with stage IA-IIA cervical cancer were randomly divided into training cohort (n=1054) and validation cohort (n=526) according to the predefined ratio of 2:1. In the training cohort, the receiver operating characteristic (ROC) curve and Youden index were used to determine the optimal threshold of HALP score for predicting cervical cancer recurrence. On this basis, the independent related factors with cervical cancer recurrence were screened through univariate and multivariate Cox regression analysis, and then a nomogram model was further established. The internal and external validation of the model was carried out in the training cohort and the validation cohort respectively through the consistency index (C-index) and calibration curve.

Results: ROC curve and Youden index showed that the optimal threshold of HALP score for predicting cervical cancer recurrence was 39.50. Multivariate analysis confirmed that HALP score and some other classic clinicopathological parameters were independently associated with cervical cancer recurrence. Based on the results of multivariate analysis, a nomogram model for predicting cervical cancer recurrence was successfully constructed. The internal and external calibration curves showed that the fitting degree of the model was good, and the C-index (the C-index of the training cohort and the validation cohort were 0.862 and 0.847, respectively) showed that the prediction accuracy of the model proposed in this study was better than other similar models.

Conclusion: HALP score may be a novel predictor for predicting the cervical cancer recurrence. Nomogram model based on HALP score and classical clinicopathological parameters can better predict the recurrence of cervical cancer.

Keywords: HALP score, nomogram model, predict, cervical cancer, recurrence

Introduction

Cervical cancer is one of the most common cancers of the female reproductive system.[1] Although the maximum 5-year overall survival rate of some patients with early-stage cervical cancer can reach more than 85% after effective treatment, recurrence is still one of the main causes of death of most patients with cervical cancer.[2] It is reported in the literature that the postoperative recurrence rate of patients with early operable cervical cancer fluctuates between 10% and 30%.[3] At present, the indicators or models for predicting recurrence of cervical cancer patients still mainly depend on traditional clinicopathological parameters, such as International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, histological grade, lymph node status, depth of invasion, etc.[4] However, relevant studies have reported that many patients

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in early stage (such as stage IA) have a short postoperative recurrence time and poor prognosis, while some advanced stage patients have a long survival time.[5] This finding to some extent shows that it may not be able to accurately evaluate the prognosis of patients (especially relatively early-stage patients) only by clinicopathological parameters such as FIGO stage. Therefore, looking for novel predictors independent from clinicopathological parameters to carry out more accurate risk stratification and reasonable individualized treatment for patients is the key to reduce recurrence and improve survival.[5]

There has been evidence reported that inflammatory response and nutritional status are closely related to tumor progression.[6] On the one hand, cytokines produced by chronic inflammation promote the occurrence and development of tumors through a series of pathophysiological processes.[7,8] On the other hand, malnutrition can lead to impaired immune function, increased inflammatory response and increased treatment side effects in cancer patients.[9] In addition, malnutrition can reflect the high metabolic activity of tumors.[10] In view of this, a variety of inflammatory or nutritional prognosis indexes including systemic inflammation response index (SIRI), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR) and prognostic nutrition index (PNI) have been developed to predict the prognosis of various tumors including cervical cancer, and these prognosis indexes show good prognostic value.[5,11,12] However, the above prognostic index only focuses on one of the inflammatory response or nutritional status, and in clinical practice, we may need to comprehensively evaluate the inflammatory response and nutritional status of patients.[6] Hemoglobin, albumin, lymphocyte, and platelet (HALP) index is a new score based on the combination of inflammation and nutritional status.[13,14] It has been found that this index can improve the prediction accuracy of the prognosis of various cancers.[15] However, up to now, studies on the impact of this index on the prognosis of cervical cancer are still very rare.

Therefore, the purpose of this study is to evaluate the prognostic value of HALP score in patients with operable cervical cancer, and establish a nomogram model combined with classical clinicopathological parameters to predict the recurrence of patients and guide the personalized treatment of patients.

Materials and Methods

Study Population

Patients with stage IA-IIA cervical cancer (according to the 2009 FIGO guidelines[16]) who received radical hysterectomy + pelvic lymph node dissection ± abdominal aortic lymph node dissection in the First Affiliated Hospital of Chongqing Medical University from January 2014 to December 2018 were included in the study. The exclusion criteria of patients are as follows: (1) without standard surgery; (2) receiving adjuvant therapy before surgery; (3) preexisting significant inflammatory conditions or immune system disorders; (4) with other malignancies; (5) with incomplete medical records; (6) lost follow-up.

According to the results of postoperative pathological examination, the patient would be recommended to receive follow-up or corresponding adjuvant treatment (radiotherapy or concurrent radiotherapy and chemotherapy). In short, when patients meet the Sedlis criteria (ie, stromal invasion, LVSI, primary tumor size) or were combined with other risk factors including poor tumor histology (such as adenocarcinoma), it was recommended that the patient received radiotherapy with (or without) concurrent chemotherapy, while when patients were combined with any high-risk factors (positive margin, parametric involvement, or lymph node metastasis), it was strongly recommended that the patient received concurrent chemoradiotherapy.[17] Radiotherapy was mainly pelvic external radiotherapy (total dose 45–50Gy, 1.8–2Gy x 25 fractions, 5 fractions/week, 5 weeks in total). If patients were combined with positive or close vaginal surgical margins, additional vaginal brachytherapy (total dose 11–18Gy, 5.5–6gy x 2–3 fractions, 2 fractions/week, 1–2 weeks in total) was also required. Radiotherapy generally started around 6–8 weeks after surgery. The concurrent chemotherapy regimen mainly included cisplatin (40 mg/m^2/week) or carboplatin (if patients were cisplatin intolerant), with a total of 6 cycles.

The postoperative follow-up plan of patients was as follows: once every 3 months in the first 2 years, once every 6 months in the next 3 years, and once a year thereafter.[2] The follow-up plan included regular physical examination and necessary auxiliary examinations. The deadline for follow-up of this study was December 2021. Except for a few dead patients during the follow-up period, the follow-up time of other patients was guaranteed to be more than 3 years. The recurrence was confirmed by more than two gynecological oncologists through physical examination, biochemical indicators, imaging

examination and pathological biopsy.[18] Recurrence included local recurrence (vaginal stump recurrence and central pelvic recurrence) and distant metastasis (upper paraaortic lymph node metastasis, peritoneal metastasis, and metastasis to other organs).[19] Recurrence-free survival (RFS) was defined as the time from the date of surgery to the date of recurrence confirmation, and overall survival (OS) was defined as the time from the date of surgery to the end of death or follow-up.[20]

Data Collection

The relevant case data of patients who met the inclusion and exclusion criteria were collected completely, including age, body mass index, preoperative hematological markers of inflammation and nutritional status (lymphocyte, neutrophil, monocyte, platelet, hemoglobin, and albumin), detailed surgical procedures, postoperative adjuvant therapy and post-operative pathological examination results (tumor site and size, histological findings, the depth of cervical stromal invasion, number of dissected and positive lymph nodes, the status of LVSI and parametrial invasion, and tumor involvement of the resection margin, etc.). Preoperative hematological markers were measured one week before the operation.[5] The postoperative pathological examination results were jointly evaluated by two pathological experts from the pathological experiment center of Chongqing Medical University according to the unified pathological analysis process and truthfully recorded in the electronic medical record system.[6] NLR, PLR, MLR, SIRI, PNI and HALP were calculated as follows: NLR=neutral count/lymphocyte count; PLR, platelet count/lymphocyte count; MLR, monocyte count/lymphocyte count; SIRI=neutrophil count × monocyte count/lymphocyte count; PNI= albumin × total lymphocyte count × 109/L; HALP= hemoglobin × albumin × lymphocyte/platelet.[5,12,15]

Study Design and Statistical Analysis

The study design was shown in Figure 1, which was roughly divided into three steps: division of patient cohort, establishment and (internal and external) validation of the model, determination of risk threshold of the model and comparison of different models. SPSS software (version 25.0, IBM statistics, Chicago, Illinois, USA) and R software (version 4.0.3, http://www.r-project.org) (Supplementary Materials R).

First, the process of division of patient cohort was as follows: the patients included in this study were randomly divided into training cohort and validation cohort according to the predefined ratio of 2:1 through the caret function of R software.[21] The training cohort was used to construct the model and verify the model internally, while the validation cohort was used for external verification of the model.[6] The differences between the basic parameters of the two cohorts were compared: the categorical variables were compared by chi-square test; *t*-test and rank sum test were used to compare continuous variables. P value <0.05 was considered as a statistically significant difference.

Secondly, the establishment and (internal and external) validation of the model was as follows: in the training cohort, the optimal threshold of the HALP score for predicting cervical cancer recurrence was determined by using the receiver operating characteristic (ROC) curve and the maximum value of Youden index (Youden index = sensitivity + specificity −1).[22,23] The prognostic value of HALP score and other predictors was compared by the area under the curve (AUC). Then the HALP score and classical clinicopathological parameters were put into univariate and multivariable Cox regression analysis to screen the independent related factors with cervical cancer recurrence (only the predictors with P value <0.05 in univariate analysis would be further included in the multivariate analysis). Based on the factors with P value <0.05 in multivariate analysis, a nomogram model was established by using R software.[5] Finally, the calibration curve and consistency index (C-index) were used to verify the model internally and externally in the training cohort and the validation cohort, respectively.[24,25]

Finally, the process of determining the risk threshold of the model and comparing different models was as follows: considering that the recurrence time of most patients with recurrent cervical cancer is concentrated within 3 years after operation, so the 3-year RFS rate of each patient was calculated by the constructed nomogram, and the optimal threshold (risk threshold) of the 3-year RFS rate calculated by the nomogram was determined by using the ROC curve and the maximum value of Youden index. According to the risk threshold of the model, the patients were further divided into high-risk group and non-high-risk group, and the survival differences between the two groups were compared. Finally, the nomogram proposed in this study was compared with similar models proposed by other studies through C-index to further prove the superiority of the model proposed in this study.[6]

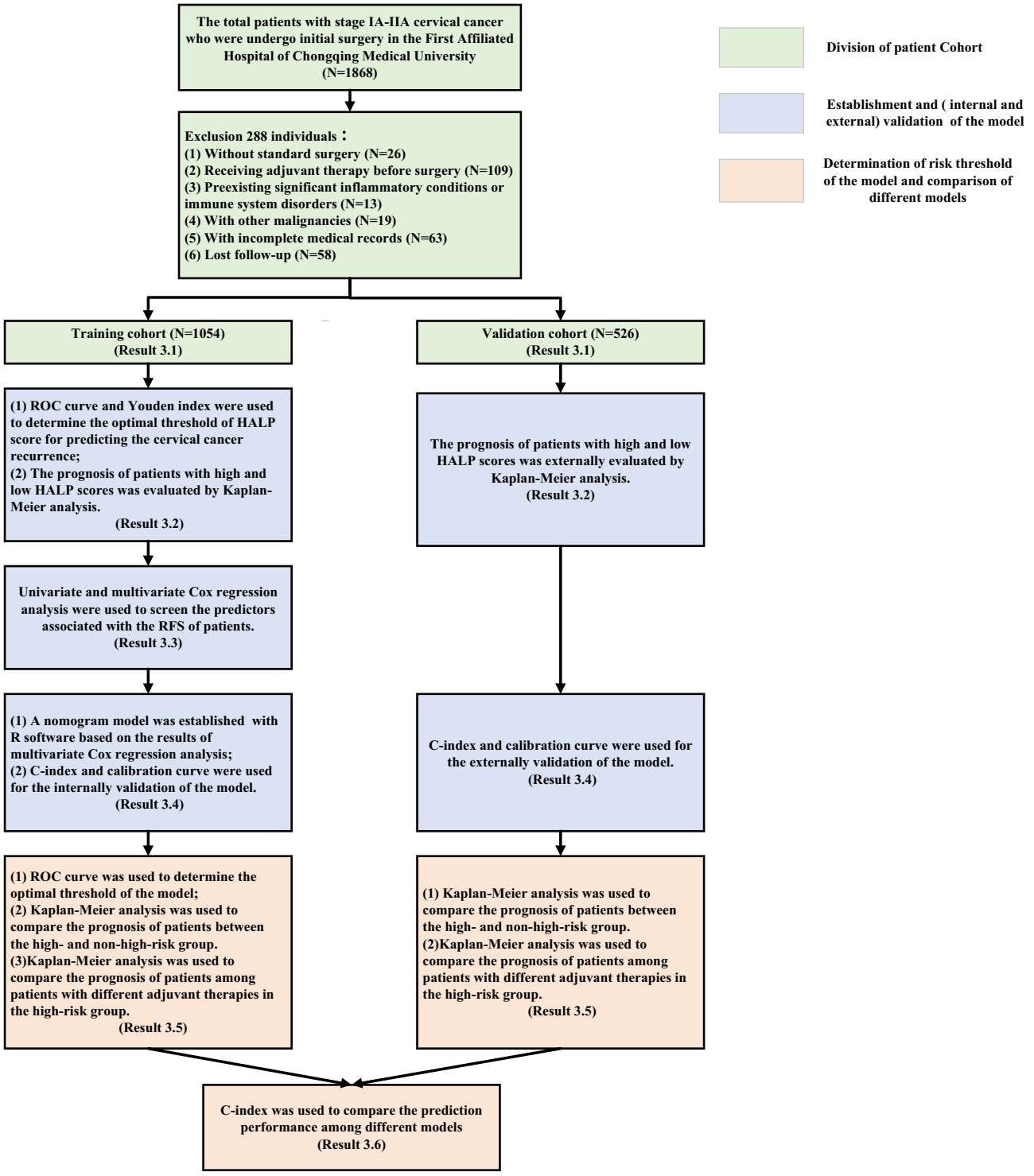

Figure 1 Study design and the flow chart of patient inclusion.

Results

Comparison of Baseline Characteristics of Patients Between Two Cohorts

As shown in Table 1, 1054 and 526 patients were finally included in the training cohort and the validation cohort, respectively. The median age of the patients was 47 (range 21–79) years old and 48 (range 24–79) years old, respectively. In the training cohort, there were 126 (11.9%), 511 (48.5%) and 417 (39.6%) patients in stage IA, IB and IIA,

Table 1 Baseline Characteristics of Patients in Two Cohorts

Variable	Training Cohort N = 1054	%	Validation Cohort N = 526	%	P-value*
Age (yrs)					0.398
Mean (±SD)	48.05 (±9.146)		48.47 (±9.182)		
Median (range)	47.00 (21–79)		48.00 (24–79)		
BMI (kg/m^2)					0.867
Mean (±SD)	23.34 (±3.19)		23.31 (±3.07)		
Median (range)	23.09 (12.02–38.97)		23.06 (14.57–36.05)		
FIGO stage					0.874
IA	126	11.9	64	12.2	
IB	511	48.5	261	49.6	
IIA	417	39.6	201	38.2	
Tumor size (cm)					0.438
<4	709	67.3	364	69.2	
≥4	345	32.7	162	30.8	
Histological type					0.581
Squamous cell carcinoma	873	82.8	430	81.7	
Adenocarcinoma	149	14.1	83	15.8	
Other types	32	3.1	13	2.5	
Histological grade					0.972
1	346	32.8	174	33.1	
2	593	56.3	293	55.7	
3	115	10.9	59	11.2	
Depth of invasion					0.652
<1/2	655	62.1	333	63.3	
≥1/2	399	37.9	193	36.7	
Parametrial invasion					0.581
No	1012	96.0	508	96.6	
Yes	42	4.0	18	3.4	
LVSI					0.868
Negative	903	85.7	449	85.4	
Positive	151	14.3	77	14.6	
Lymph node metastasis					0.861
No	925	87.8	460	87.5	
Yes	129	12.2	66	12.5	
Resection margin involvement					0.573
No	1038	98.5	516	98.1	
Yes	16	1.5	10	1.9	
Type of surgical procedure					0.400
LRH	950	90.1	481	91.4	
ARH	104	9.9	45	8.6	
Adjuvant treatment					0.979
Follow-up	362	34.3	185	35.2	
Only radiotherapy	377	35.8	187	35.6	
Only chemotherapy	98	9.3	46	8.7	
Chemoradiotherapy	217	20.6	108	20.5	
Recurrence					0.330
No	952	90.3	483	91.8	
Yes	102	9.7	43	8.2	
Sites of relapsed					0.818
Vaginal stump	12	11.8	8	18.6	
Central pelvic region	42	41.2	16	37.2	

(*Continued*)

Table 1 (Continued).

Variable	Training Cohort N = 1054	%	Validation Cohort N = 526	%	P-value*
Lymph nodes (upper para-aortic)	21	20.6	7	16.3	
Peritoneal metastases	8	7.8	3	7.0	
Metastasis to other organs	19	18.6	9	20.9	
Death					0.813
Death of recurrence	60	5.7	26	4.9	
Death of other reasons	9	0.8	5	1.0	
Alive	985	93.5	495	94.1	
RFS time (months)					0.489
Mean (±SD)	55.41 (±20.67)		56.17 (±20.57)		
Median (range)	53.00 (6–96)		53.00 (8–96)		
Follow-up (months)					0.541
Mean (±SD)	56.70 (±18.94)		57.32 (±18.92)		
Median (range)	53.00 (9–96)		54.00 (7–91)		

Notes: *The comparison of the parameters between the training cohort and the validation cohort.
Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphatic vessel space invasion; LRH, laparoscopic radical hysterectomy; ARH, abdominal radical hysterectomy; RFS, recurrence-free survival.

respectively. Similarly, in the validation cohort, there were 64 (12.2%), 261 (49.6%) and 201 (38.2%) patients in stage IA, IB and IIA, respectively. Squamous cell carcinoma was the main histological type of patients in the two cohorts (accounting for more than 80%), followed by adenocarcinoma (accounting for about 15%) and other types (accounting for less than 5%). In the training cohort, 692 (65.7%) patients received adjuvant therapy after surgery, of which 377 (35.8%) and 217 (20.6%) patients received radiotherapy and concurrent chemoradiotherapy respectively, while 98 (9.3%) patients refused to receive radiotherapy due to personal factors and only received chemotherapy. The proportion of patients receiving different adjuvant therapies in the validation cohort was similar to that in the training cohort.

The median follow-up time of patients in the two cohorts was 53 months (range 9–96) and 54 months (range 7–91), respectively. During the follow-up period, 102 (9.7%) recurred and 69 (6.5%) died in the training cohort, of which 60 died of recurrence and 9 died of other causes; in the validation cohort, 43 (8.2%) recurred and 31 (5.9%) died, of which 26 died of recurrence and 5 died of other causes. The distribution of baseline characteristics of patients in the two cohorts was relatively consistent, and there was no statistically significant difference (P values of all parameters between the two cohorts were >0.05).

Prognostic Value of HALP Score in Predicting Recurrence of Cervical Cancer

The distribution of preoperative hematological markers and several inflammatory or nutritional prognosis index based on preoperative hematological markers was shown in Table 2. The ROC curve and the maximum value of the Youden index showed that the optimal threshold of HALP score for predicting cervical cancer recurrence was 39.50, and the AUC (0.658) of HALP score was greater than other similar inflammatory or nutritional prognosis indexes, including SIRI (AUC=0.634), NLR (AUC=0.599), MLR (AUC= 0.589), PLR (AUC=0.624) and PNI (AUC=0.618) (Figure 2). The survival curve showed that the RFS rate and OS rate of patients with low HALP score (HALP score<39.50) in the two cohorts were significantly lower than those with high HALP score (HALP score ≥ 39.50) (Figure 3). However, the predictive value of using the HALP score alone to predict cervical cancer recurrence was not prominent since the C-index of the HALP score in the training cohort and the validation cohort was only 0.640 (95% CI, 0.583–0.696) and 0.611 (95% CI, 0.525–0.698), respectively.

Univariate and Multivariate Cox Regression Analysis of Predicting Recurrence of Cervical Cancer

As shown in Table 3, univariate Cox regression analysis showed that HALP score (P<0.001), tumor size (P<0.001), histological type (P<0.001), histological grade (P<0.001), depth of invasion (P<0.001), parametric invasion (P<0.001), LVSI (P<0.001),

Table 2 The Distribution of Several Inflammatory Prognosis Indexes of Patients in Two Cohorts

Variable	Training Cohort N =1054	%	Validation Cohort N = 526	%	P value*
Lymphocyte (10^9/L)					0.610
Mean (±SD)	1.69 (±0.53)		1.71 (±0.53)		
Median (range)	1.66 (0.35–3.89)		1.68 (0.42–3.55)		
Neutrophil (10^9/L)					0.624
Mean (±SD)	3.51 (±1.46)		3.55 (±1.47)		
Median (range)	3.24 (0.93–12.36)		3.24 (1.06–11.42)		
Monocyte (10^9/L)					0.692
Mean (±SD)	0.36 (±0.13)		0.36 (±0.13)		
Median (range)	0.34 (0.01–0.95)		0.34 (0.01–0.88)		
PLT (10^9/L)					0.808
Mean (±SD)	216.36 (±65.10)		217.21 (±65.82)		
Median (range)	205.00 (66.00–588.00)		206.00 (80.00–514.00)		
Hemoglobin (g/L)					0.967
Mean (±SD)	118.34 (±17.04)		118.31 (±17.26)		
Median (range)	122.00 (65.00–169.00)		122.00 (58.00–159.00)		
Albumin (g/L)					0.805
Mean (±SD)	42.46 (±4.08)		42.51 (±3.95)		
Median (range)	43.00 (24.00–64.00)		43.00 (27.00–58.00)		
NLR					0.922
Mean (±SD)	2.31 (±1.63)		2.32 (±1.58)		
Median (range)	1.91 (0.56–27.16)		1.89 (0.58–15.61)		
MLR					0.506
Mean (±SD)	0.23 (±0.10)		0.22 (±0.10)		
Median (range)	0.21 (0.01–1.14)		0.20 (0.02–0.91)		
PLR					0.639
Mean (±SD)	141.00 (±68.01)		139.35 (±62.18)		
Median (range)	126.00 (31.25–617.65)		124.60 (34.78–580.95)		
SIRI					0.767
Mean (±SD)	0.86 (±0.77)		0.85 (±0.67)		
Median (range)	0.68 (0.04–13.85)		0.68 (0.07–7.03)		
PNI					0.528
Mean (±SD)	72.01 (±23.83)		72.82 (±24.15)		
Median (range)	70.06 (13.05–167.27)		71.75 (16.80–166.85)		
HALP score					0.790
Mean (±SD)	43.47 (±22.10)		43.79 (±22.15)		
Median (range)	40.95 (6.06–185.60)		41.19 (6.54–171.58)		
<39.50	480	45.5	234	44.5	
≥39.50	574	54.5	292	55.5	

Note: *The comparison of the parameters between the training cohort and the validation cohort.
Abbreviations: PLT, platelet; SIRI, systemic inflammation response index; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PNI, prognostic nutrition index; HALP, hemoglobin, albumin, lymphocyte, and platelet.

lymph node metastasis (P<0.001), reaction margin involvement (P<0.001) and adjuvant treatment (P=0.001) were related factors to cervical cancer recurrence, these factors were further included in the multivariate Cox regression analysis. While age (P=0.652), BMI (P=0.251), FIGO stage (P=0.419) and type of surgical procedure (P=0.873) were excluded from the multivariate analysis because the P values of them in the univariate Cox regression were greater than 0.05.

Further multivariate analysis found that the above ten factors were still independently associated with the recurrence of cervical cancer, including HALP score (P<0.001), tumor size (P<0.001), histological type (P<0.001), histological grade (P=0.001), depth of invasion (P=0.002), parametric invasion (P<0.001), LVSI (P=0.005), lymph node metastasis (P<0.001), reaction margin involvement (p=0.007) and adjuvant treatment (p=0.008). These ten predictors were further used to develop nomogram model.

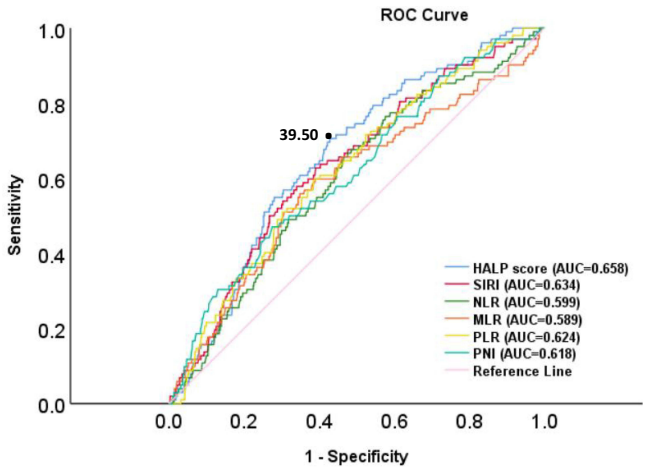

Figure 2 The ROC curve of HALP score for predicting the recurrence of cervical cancer.
Notes: "black dot" represents the area under the curve (AUC) at this point is the largest, which suggests that the value of this point is the optimal threshold of the indicator for predicting the recurrence of cervical cancer.

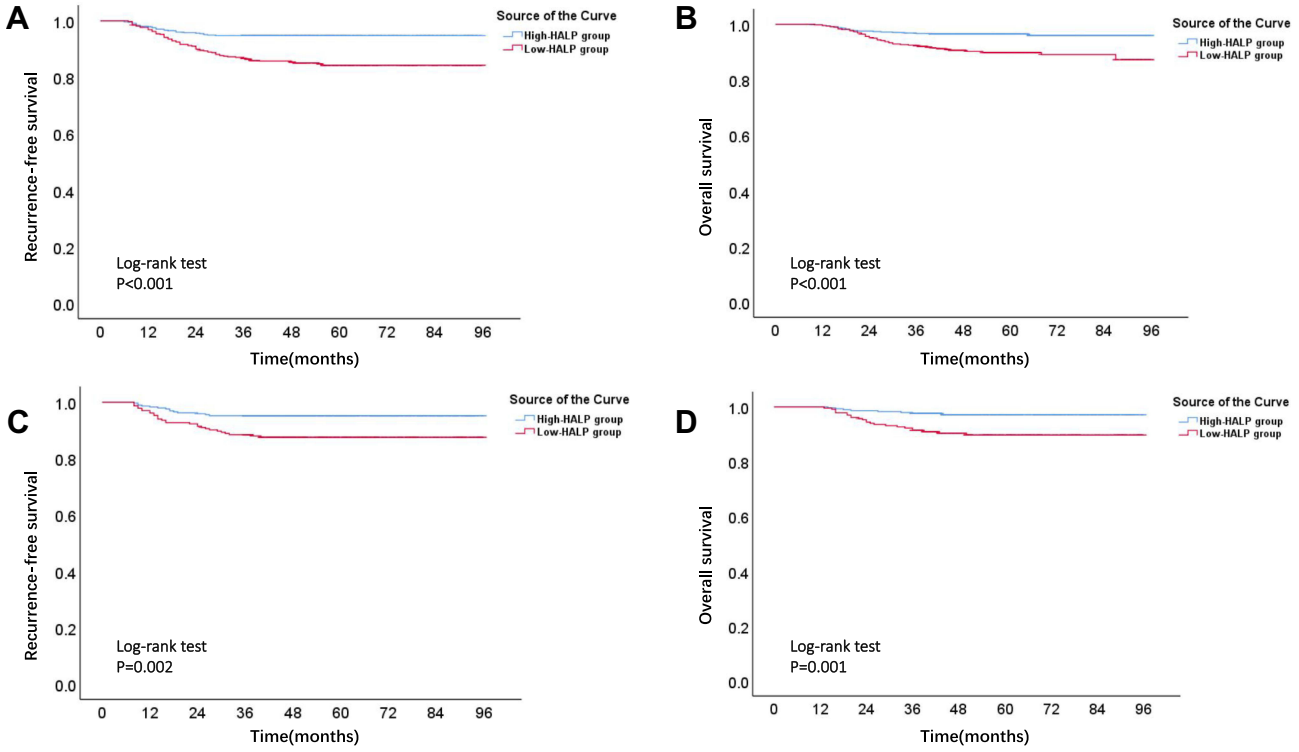

Figure 3 Kaplan–Meier survival curve of patients with low and high HALP score in two cohorts.
Notes: (**A**) RFS curve and (**B**) OS curve of patients with low and high HALP score in the training cohort; (**C**) RFS curve and (**D**) OS curve of patients with low and high HALP score in in the validation cohort.

Establishment and Validation of the Nomogram Model

As mentioned above, the nomogram model was successfully constructed based on 10 predictors (HALP score and nine other clinicopathological parameters) with P values <0.05 in the multivariate analysis (Figure 4). The length of the line segment corresponding to each predictor in the nomogram represents the weight of the predictor causing cervical cancer recurrence. From the nomogram, we could see that even compared with classical clinicopathological parameters, the HALP score still occupied a large weight, which indicated that the HALP score might be a potentially important prognostic factor for cervical cancer recurrence. At the same time, ROC curves showed that whether in the training

Table 3 Univariate and Multivariate Analysis of Factors Predicting Cervical Cancer Recurrence in the Training Cohort

Variables	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Age	1.005	0.984–1.026	0.652			
BMI	0.964	0.905–1.026	0.251			
FIGO stage						
IA	1.000		0.419			
IB	1.346	0.660–2.742	0.414			
IIA	1.579	0.772–3.230	0.211			
Type of surgical procedure (ARH vs LRH)	0.948	0.493–1.821	0.873			
Tumor size (≥4 vs <4)	3.289	2.214–4.886	<0.001	2.787	1.828–4.249	<0.001
Histological type (NSCC vs SCC)	2.148	1.403–3.289	<0.001	2.365	1.483–3.773	<0.001
Histological grade						
1	1.000		<0.001	1.000		0.001
2	1.909	1.139–3.198	0.014	1.758	1.024–3.019	0.041
3	3.941	2.146–7.237	<0.001	3.218	1.698–6.095	<0.001
Depth of invasion (≥1/2 vs <1/2)	3.534	2.341–5.334	<0.001	2.206	1.347–3.612	0.002
Parametrial invasion (Yes vs No)	5.477	3.210–9.344	<0.001	3.602	2.031–6.388	<0.001
LVSI (Positive vs Negative)	5.028	3.393–7.452	<0.001	1.915	1.231–3.023	0.005
Lymph node metastasis (Yes vs No)	8.464	5.736–12.488	<0.001	3.735	2.399–5.813	<0.001
Resection margin involvement (Yes vs No)	5.566	2.583–11.996	<0.001	3.164	1.362–7.346	0.007
Adjuvant treatment (Yes vs No)	2.378	1.445–3.915	0.001	0.452	0.251–0.814	0.008
HALP score (<39.50 vs ≥39.50)	2.978	1.945–4.559	<0.001	2.446	1.581–3.785	<0.001

Abbreviations: CI, confidence interval; LRH, laparoscopic radical hysterectomy; ARH, abdominal radical hysterectomy; LVSI, lymphatic vessel space invasion; HALP, hemoglobin, albumin, lymphocyte, and platelet; SCC, squamous cell carcinoma; NSCC, non-squamous cell carcinoma, including adenocarcinoma and other types.

cohort or the validation cohort, adding HALP score on the basis of classic clinicopathological parameters greatly improved the prediction accuracy of the model compared with a single predictor (only HALP score or only clinicopathological parameters) (Figure 5).

The internal and external validation of the model was mainly evaluated by the calibration curve and C-index. As can be seen from Figure 6, the internal and external calibration curves of 1-, 3- and 5-years showed that the "nomogram predicted survival" is highly consistent with the "actual survival", which indicated that the model fit well. The C-index of internal and external validation of the model also showed that the model had a pretty good prediction accuracy, the C-index of training cohort and validation cohort were 0.862 (95% CI, 0.806–0.919) and 0.847 (95% CI, 0.760–0.934), respectively.

Optimal Risk Thresholds of the Nomogram Model

The 3-year RFS rate of each patient was calculated through the nomogram, and the optimal threshold of the 3-year RFS rate of patients predicted by the nomogram (the risk threshold of the model) was determined to be 0.86 by using the ROC curve and the maximum value of Youden index (Figure 7). Then, according to the risk threshold of the model, all patients in the two cohorts were divided into high-risk group (3-year RFS rate <0.86) and non-high-risk group (3-year RFS rate ≥ 0.86) of cervical cancer recurrence. Kaplan Meier survival analysis showed that the RFS rate and OS rate of patients in the high-risk group were much lower than those in the non-high-risk group (P<0.001). The specific distribution of prognosis of patients in the two groups was shown in Table 4 and Figure 8.

To further explore the prognostic value of the risk threshold of the model, the survival differences of patients receiving different adjuvant treatments (follow-up, only radiation, only chemotherapy and chemotherapy) in two groups were further compared to determine which patients could benefit from adjuvant therapy. We found the following two very clinically significant results: (1) In the non-high-risk group, there was no significant difference in survival prognosis (RFS and OS) between patients receiving adjuvant therapy and patients not receiving adjuvant therapy (Figure 9); (2) In

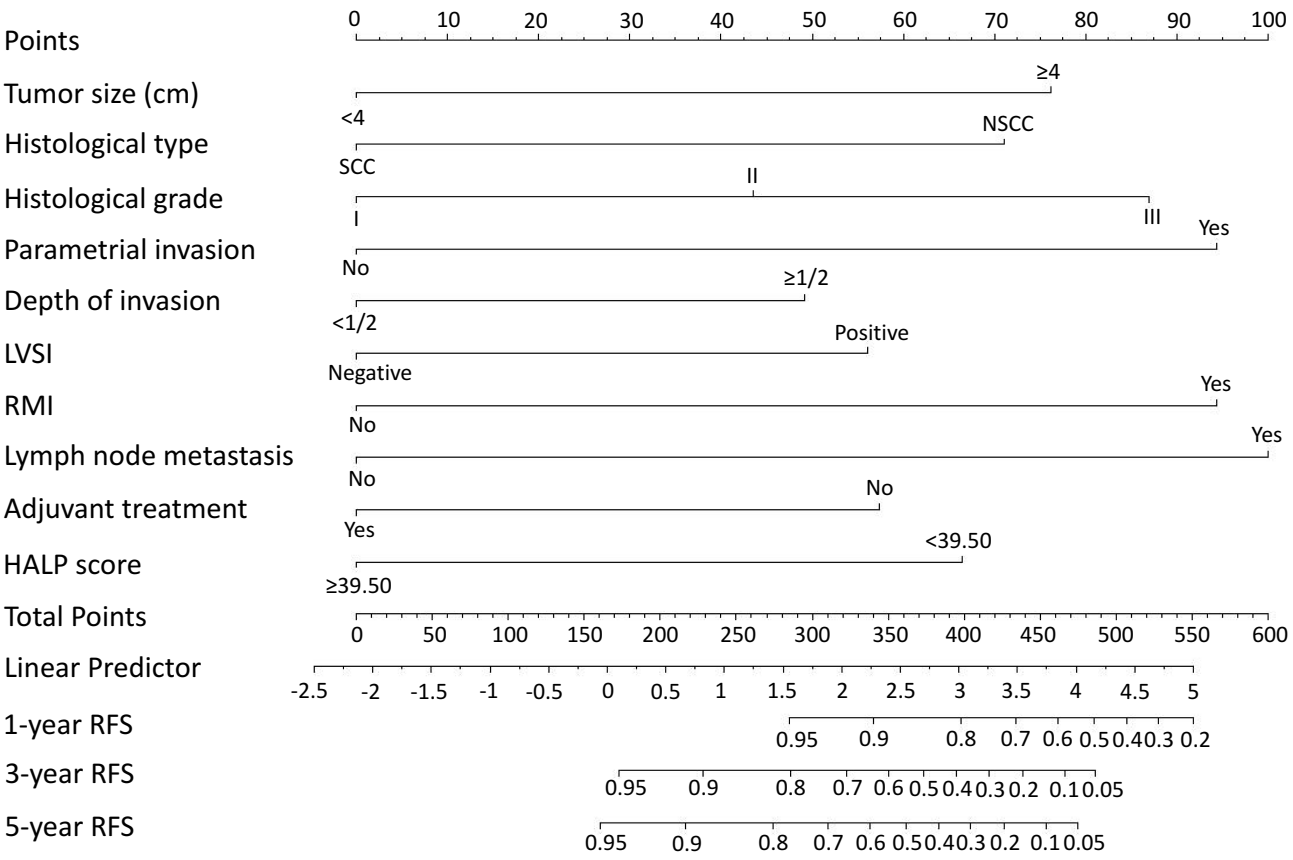

Figure 4 Nomogram model for predicting the 1-, 3-, and 5-year RFS rates of cervical cancer patients.
Notes: To predict the 1-, 3-, and 5-year RFS rates of cervical cancer patients, draw the vertical line segment to the "Points" axis to get the corresponding score of each predictor, and calculate the total score of all predictors. Draw the vertical line segment from the "Total Points" axis to the "1-year RFS", "3-year RFS", and "5-year RFS" axis to get the corresponding 1-year, 3-year and 5-year RFS rates of cervical cancer patients.
Abbreviations: LVSI, lymphatic vessel space invasion; RMI, resection margin involvement; HALP, hemoglobin, albumin, lymphocyte, and platelet; SCC, squamous cell carcinoma; NSCC, non-squamous cell carcinoma.

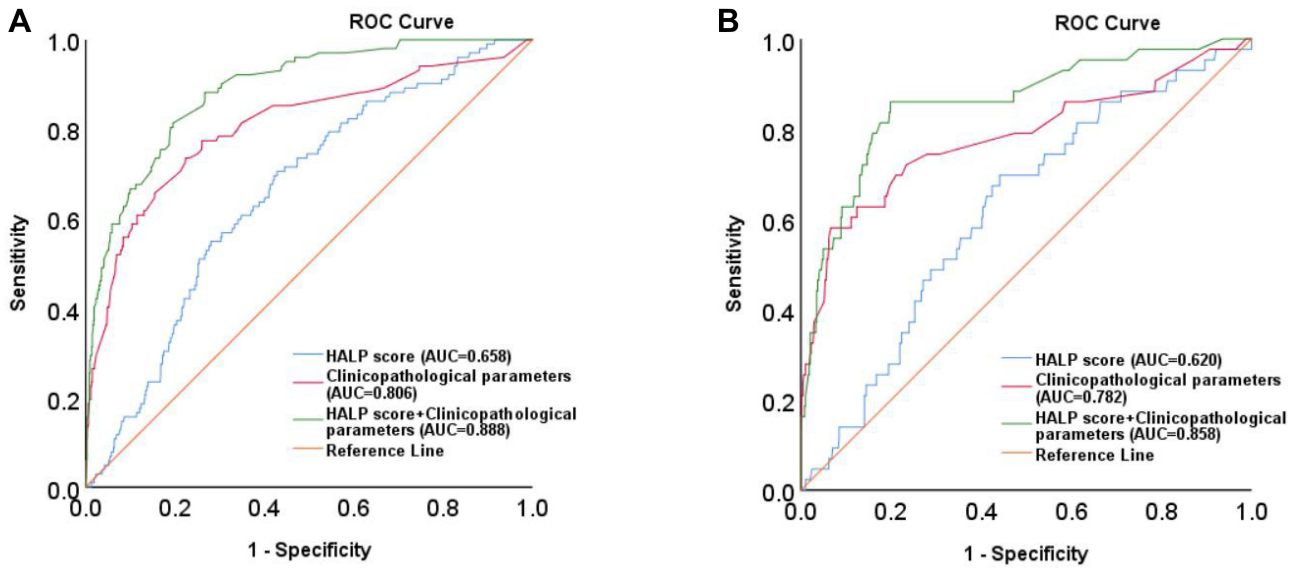

Figure 5 Area under the curve (AUC) for HALP score, clinicopathological parameters and their combination in (**A**) training cohort and (**B**) validation cohort.

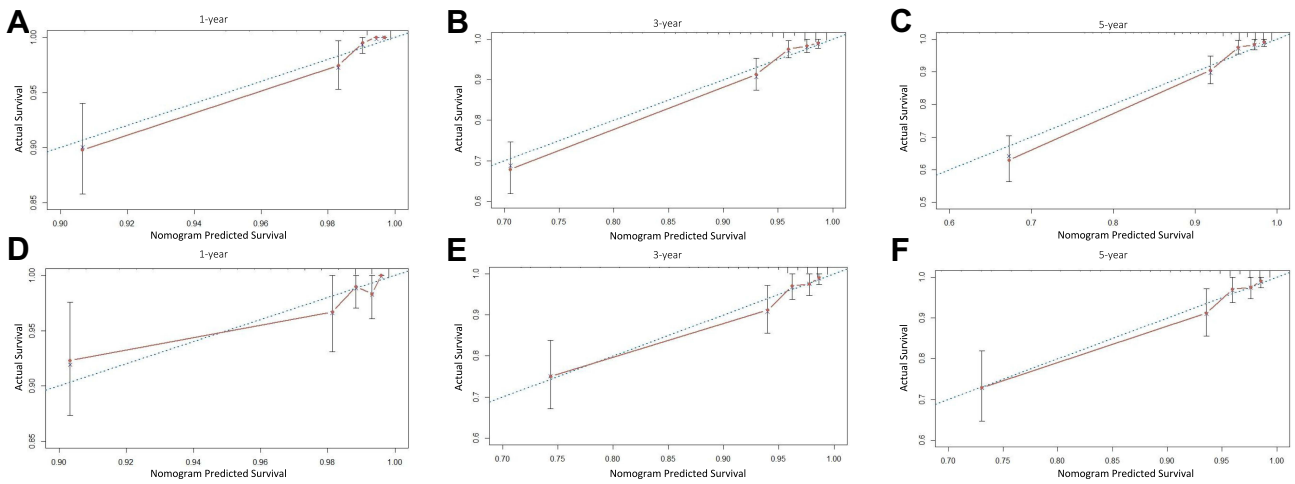

Figure 6 The calibration curve for internal and external validation of the nomogram model.
Notes: (**A–C**) The internal calibration curve and (**D–F**) the external calibration curve of the nomogram for predicting the 1-, 3-, and 5-year RFS rates of cervical cancer patients, respectively.

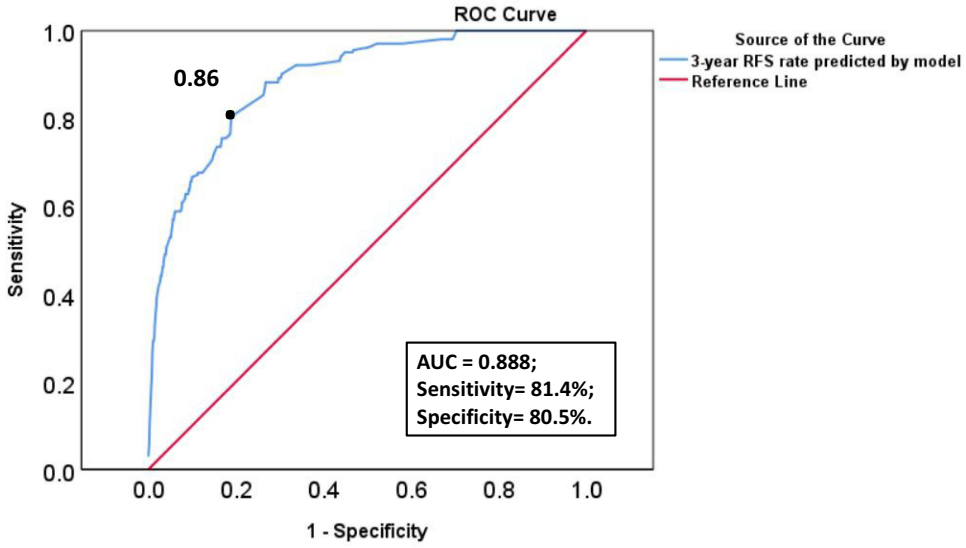

Figure 7 The ROC curve of the 3-year RFS rates (predicted by the nomogram model) for predicting the recurrence of cervical cancer.
Notes: "black dot" represents the area under the curve (AUC) at this point is the largest, which suggests that the optimal threshold of the 3-year RFS rate (risk threshold of the model) for predicting the recurrence of cervical cancer is 0.86 (AUC= 0.888; sensitivity=81.4%; specificity=80.5%).

the high-risk group, we were surprised to find that the survival prognosis of patients who received various adjuvant therapies was better than that of patients who did not receive adjuvant therapy to varying degrees. Further analysis found that the survival prognosis of patients in the high-risk group who received concurrent chemoradiotherapy was better than that of patients who received only single adjuvant therapy (only radiotherapy or only chemotherapy) (Supplementary Table 1 and Figure 10).

Comparison of Prediction Performance (C-Index) of Different Models

To further illustrate the advantages of the model proposed in this study, we compared it with the representative models proposed by other similar studies in recent years through the C-index. These models included model A[26] (an information scoring system based on PLR and album), model B[27] (a nomogram model including FIGO staging, historical type and parametric invasion) and model C[5] (a nomogram model including FIGO staging, LVSI and SIRI).

Table 4 Analysis of Survival Differences Between High-Risk and Non-High-Risk Group in Two Cohorts

Cohort	Group	Number of Recurrences	3-Year RFS Rate (95% CI)	5-Year RFS Rate (95% CI)	P-Value[a]	Number of Deaths	3-Year OS Rate (95% CI)	5-Year OS Rate (95% CI)	P-value[b]
Training Cohort (N=1054)	High-risk group (N=269, 25.5%)	83 (81.4%)	71.6% (66.1–77.1%)	68.0% (62.1–73.9%)	<0.001	53 (76.8%)	83.2% (78.7–87.7%)	79.6% (74.5–84.7%)	<0.001
	Non-high-risk group (N=785, 74.5%)	19 (18.6%)	97.7% (96.7–98.7%)	97.5% (96.3–98.7%)		16 (23.2%)	98.6% (97.8–99.4%)	98.1% (97.1–99.1%)	
Validation Cohort (N=526)	High-risk group (N=133, 25.3%)	37 (86.0%)	73.7% (66.3%-81.1%)	72% (64.4%-79.7%)	<0.001	23 (74.2%)	84.9% (78.8%-91.0%)	81.5% (74.4–88.6%)	<0.001
	Non-high-risk group (N=393, 74.7%)	6 (14.0%)	98.5% (97.3–99.7%)	98.5% (97.3–99.7%)		8 (25.8%)	98.2% (96.8–99.6%)	97.9% (96.5–99.3%)	

Note: [a]Log rank test of RFS, [b]Log rank test of OS.
Abbreviations: CI, confidence interval; RFS, recurrence-free survival; OS, overall survival.

From Table 5, we have found the following two results: (1) The C-index of model C and the model proposed in this study was above 0.8, which was better than model A and model B (the C-index was below 0.8). This may be because model C and the model proposed in this study were constructed based on the combination of classical clinicopathological parameters and systemic inflammation score, in terms of prediction performance, they were better than model A and model B, which were only composed of one of the classical clinicopathological parameters or systemic inflammation score; (2) The C-index of the model proposed in this study was the highest among the four models. Even compared with model C, which was also constructed based on clinicopathological parameters and systemic inflammation score, the model proposed in this study still had great advantages in prediction performance. This may be because that the prediction performance of the HALP score

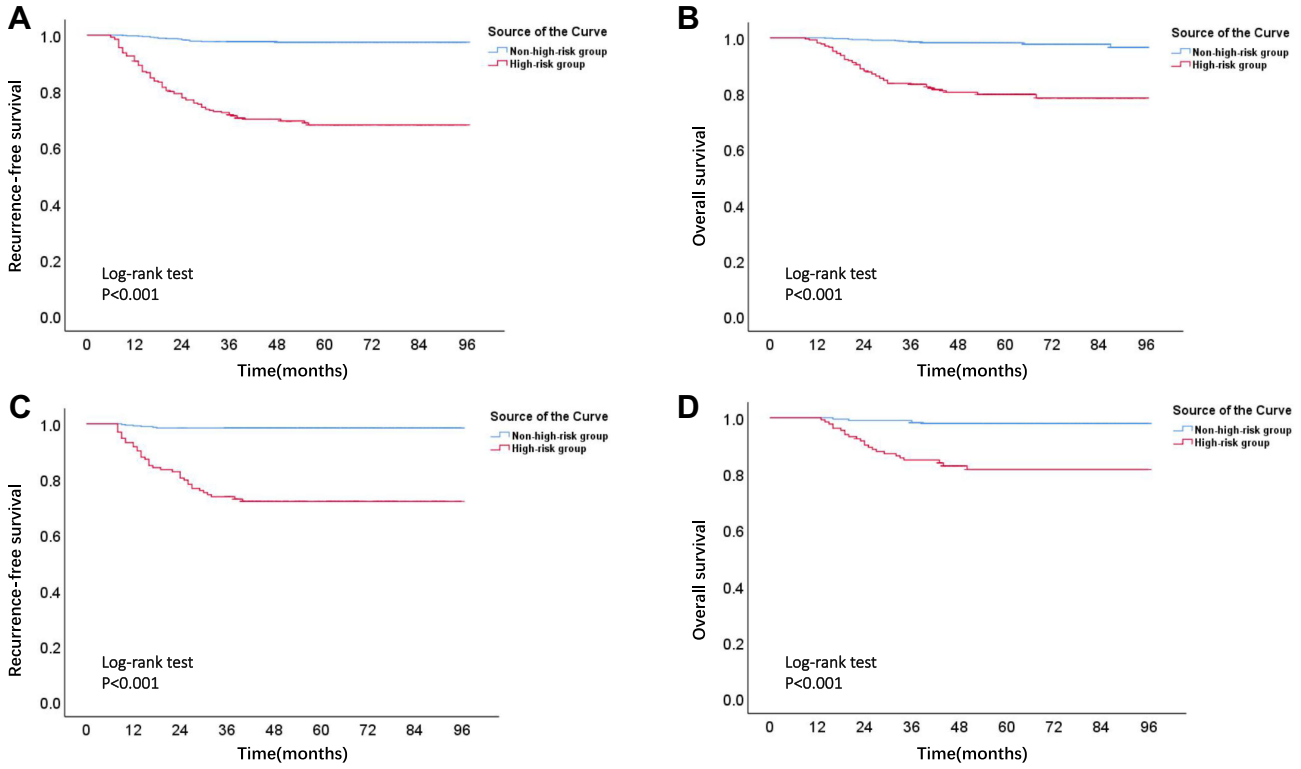

Figure 8 Kaplan–Meier survival curve of high-risk and non-high-risk groups in two cohorts.
Notes: (**A**) RFS curve and (**B**) OS curve of high-risk and non-high-risk groups in the training cohort; (**C**) RFS curve and (**D**) OS curve of high-risk and non-high-risk groups in the validation cohort.

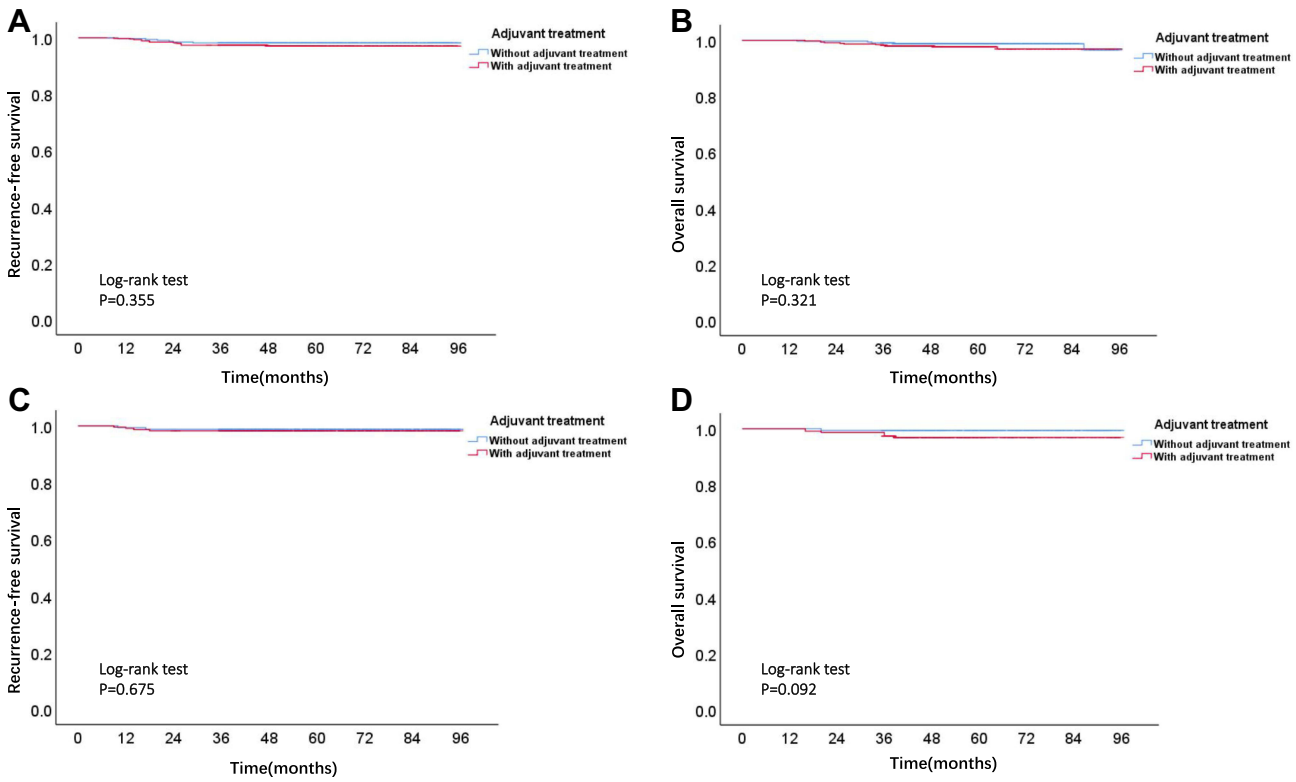

Figure 9 Kaplan–Meier survival curve of patients with or without adjuvant treatment in non-high-risk group in two cohorts.
Notes: (**A**) RFS curve and (**B**) OS curve of patients with or without adjuvant treatment in non-high-risk group in the training cohort. (**C**) RFS curve and (**D**) OS curve of patients with or without adjuvant treatment in non-high-risk group in the validation cohort.

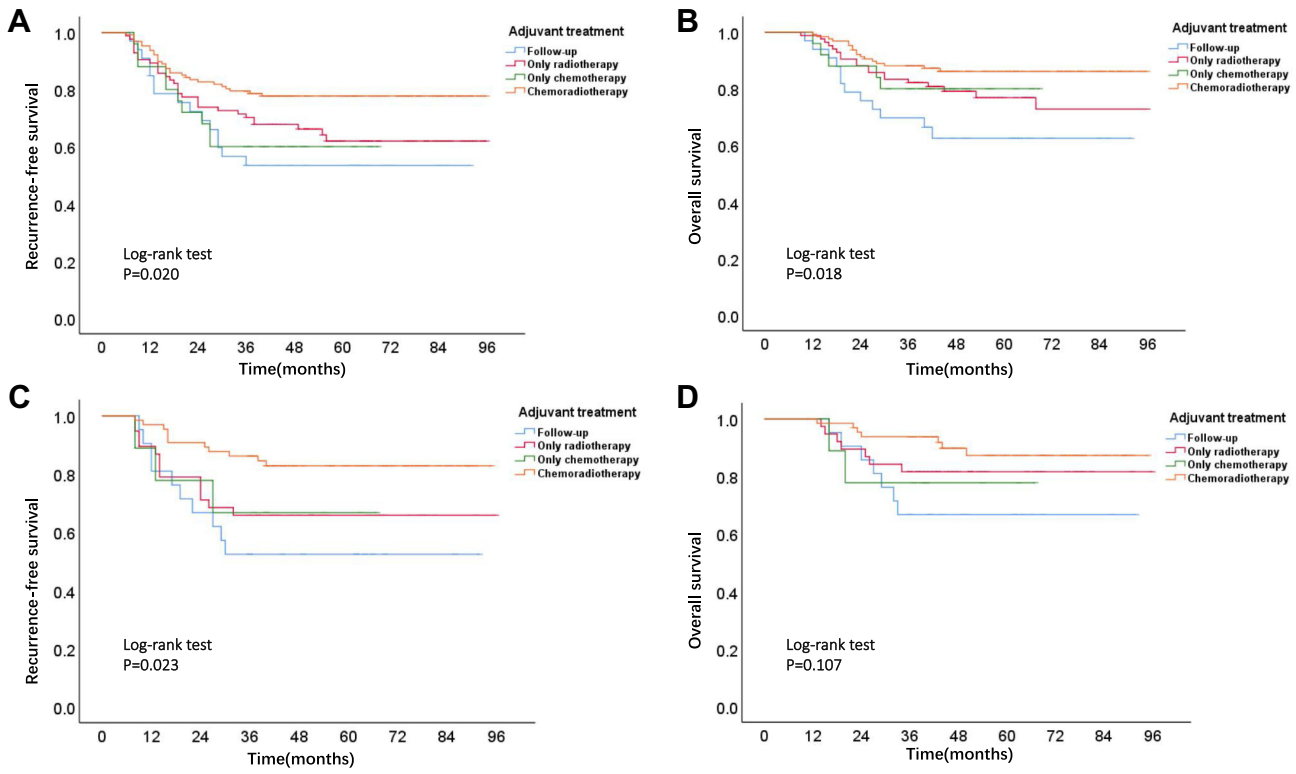

Figure 10 Kaplan–Meier survival curve of patients receiving different adjuvant treatment in high-risk group in two cohorts.
Notes: (**A**) RFS curve and (**B**) OS curve of patients receiving different adjuvant treatment in high-risk group in the training cohort. (**C**) RFS curve and (**D**) OS curve of patients receiving different adjuvant treatment in high-risk group in the validation cohort.

Table 5 The Predictive Performance (C-Index) of Several Different Models for Predicting Cervical Cancer Recurrence in Two Cohorts

Model	Author	Composition of the Model	Key Predictors of the Model	C-Index (95% CI)	
				Training Cohort	Validation Cohort
Model A	Ruru Zheng et al 2016[26]	Systemic inflammation score	An inflammation scoring system based on PLR and albumin.	0.722 (0.666–0.779)	0.682 (0.595–0.769)
Model B	Xiaoyan Tang et al 2021[27]	Clinicopathological parameters	A nomogram model including FIGO staging, histological type and parametrial invasion.	0.784 (0.728–0.840)	0.755 (0.669–0.841)
Model C	Bei Chao et al 2020[5]	Clinicopathological parameters + Systemic inflammation score	A nomogram model including FIGO staging, LVSI and SIRI	0.818 (0.762–0.875)	0.806 (0.719–0.893)
Model proposed in this study		Clinicopathological parameters + Systemic inflammation score	A nomogram model including tumor size, histological type, histological grade, depth of invasion, parametrial invasion, LVSI, lymph node metastasis, resection margin involvement, adjuvant treatment and HALP score.	0.862 (0.806–0.919)	0.847 (0.760–0.934)

Abbreviations: PLR, platelet/lymphocyte ratio; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphatic vessel space invasion; SIRI, systemic inflammation response index; HALP, hemoglobin, albumin, lymphocyte, and platelet.

incorporated in the model proposed in this study was appropriately better than that of the SIRI incorporated in model C, which has been proved in the previous 3.2 results. At the same time, the classical clinicopathological parameters included in the model proposed in this study were more comprehensive than model C.

Discussion

As we all know, recurrence can lead to poor prognosis of cervical cancer patients, so it is particularly important to accurately predict the recurrence probability of patients and carry out personalized prognosis management.[5] In this study, we first constructed the HALP score based on preoperative hematological markers. The survival curve showed that patients with high and low HALP scores have different survival prognosis (Figure 3). Univariate and multivariate analysis showed that the HALP score was an independent related factor of cervical cancer recurrence (Table 3), which suggested that we should not only pay attention to the clinicopathological characteristics of patients when evaluating the prognosis of patients, appropriate consideration should also be given to the patient's inflammatory and nutritional status, such as the HALP score.[28] Therefore, we combined the HALP score with classical clinicopathological parameters to construct a nomogram model for predicting cervical cancer recurrence (Figure 4), and ROC curve showed that the area under the curve of the combination of HALP score and classical clinicopathological parameters was better than a single predictor (Figure 5). Compared with the traditional method of roughly evaluating the recurrence risk according to clinicopathological parameters, this nomogram model can accurately predict the 1-, 3- and 5-year RFS rate of patients, which was undoubtedly very interesting and practical. At the same time, the internal and external validation of the model suggested that the model had good fitness, and the prediction performance of the model was also better than several other similar models, which further indicated that the model may have good extrapolation.

At present, whether patients should need adjuvant therapy after surgery mainly depends on whether patients are combined with intermediate- or high-risk clinicopathological factors.[20] According to the recommendations of the existing guidelines, the risk stratification of patients can be effectively carried out, so as to screen out most of the intermediate- and high-risk patients who need adjuvant treatment (radiotherapy or concurrent chemoradiotherapy). However, there are still some potentially high-risk patients who have missed adjuvant treatment.[29] For example, these patients may show relatively good clinicopathological characteristics, but in fact, they may have excessive inflammatory reaction and poor nutritional status, which may also lead to a poor prognosis for patients to a large extent.[11,12] Therefore, the

comprehensive evaluation based on the combination of clinical pathological characteristics and inflammatory nutritional status is more conducive to the personalized prognosis management of patients.[5] In this study, the nomogram model based on classical clinicopathological parameters and HALP score can carry out more detailed risk stratification and corresponding prognosis management for patients to a certain extent. Specifically, we found that the RFS rate and OS rate of patients in the high-risk group divided based on the risk threshold of the nomogram were far lower than those in the non-high-risk group (Table 4 and Figure 8), which indicated that these patients may be the beneficiaries of adjuvant therapy, and further research findings also proved our conjecture that the overall survival prognosis of patients receiving adjuvant therapy in the high-risk group was better than that of patients not receiving adjuvant therapy. The survival prognosis of patients receiving concurrent chemoradiotherapy was better than that of patients receiving single adjuvant therapy (Supplementary Table 1 and Figure 10). This result suggested that we should pay more attention to the prognosis management of these high-risk patients identified by the model. For example, for a small number of patients in the high-risk group who have not received adjuvant therapy, they should be encouraged to try to receive standard adjuvant therapy and have closer follow-up. For most of the patients in the high-risk group who received the corresponding adjuvant treatment according to the guidelines, the existing adjuvant treatment scheme may not be able to effectively control the recurrence of these patients, so it may be necessary to recommend these patients receive concurrent chemoradiotherapy (if the original adjuvant therapy scheme only includes radiotherapy) or appropriately increase the cycle of adjuvant therapy. Of course, encouraging patients to try more diversified adjuvant therapies (such as targeted drug therapy or immunotherapy) is also a good choice.[30]

It is worth mentioning that in a recent similar study, Kittinun et al also found that a lower HALP score was an independent predictor of poorer oncological outcomes in a cohort of 1588 locally advanced cervical cancer (LACC) patients who received radiotherapy or chemoradiotherapy.[10] This result is similar to our study, and also shows that HALP score has important prognostic significance not only in early operable patients, but also in LACC patients who received adjuvant therapy only. Meanwhile, the study also proposed that the addition of the HALP index can improve the accuracy of predicting the oncological outcomes of LACC patients, which is undoubtedly consistent with our research results. The difference between two studies is that our study has provided a specific prediction model based on the HALP score and classical clinicopathological parameters. Based on this model, patients with high risk of recurrence can be well distinguished and personalized prognosis management can be performed for patients.

The biggest limitation of this study was that it was a single-center retrospective study. Although our sample size was large enough, the model still needs multicenter prospective validation to better promote externally.[31] Secondly, due to the limitations of the retrospective study and the patients included in this study from 2014 to 2018, the 2009 FIGO stage was still used in this study, which lead to a certain degree of lag. Compared with the 2009 FIGO stage, the 2018 FIGO stage adopts pathological factors for the first time and has been incorporated into the NCCN guidelines to guide the prognosis of patients, which means that the staging criteria of cervical cancer has changed from a clinical staging system to a pathological staging system.[17,32] Finally, a small number of patients were lost to follow-up during the follow-up period. Although the number of patients lost to follow-up is small, it may still cause some bias to the study results.

In conclusion, in this study, we explored the prognostic value of the HALP score based on preoperative hematological markers in cervical cancer and established a model to predict the recurrence of cervical cancer. Based on this model, we can carry out more detailed risk stratification for patients, so as to carry out personalized prognosis management for patients.

Abbreviations

PLT, platelet; SIRI, systemic inflammation response index; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet/lymphocyte ratio; HALP, hemoglobin, albumin, lymphocyte and platelet; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphatic vessel space invasion; HT, hormonal treatment; RFS, recurrence-free survival; OS, overall survival; ROC, receiver operating characteristic; AUC, area under the curve; NCCN, National Comprehensive Cancer Network.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethics Committee of Chongqing Medical University approved this study (Ethics approval number:2021-174). All patients provided their informed consent before starting the treatment and gave consent to have their data published. As it was a retrospective clinical study, all the patients were contacted by telephone to obtain verbal informed consent and it was approved by the ethics committee. All data about the patients was anonymized or maintained with confidentiality. This study complied with the Declaration of Helsinki.

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Disclosure

The authors declared no conflicts of interest in this study.

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