

Original Article

Preoperative SII combined with tumor markers for predicting postoperative recurrence in cervical cancer

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Abstract: Objective: We aimed to explore whether integrating preoperative systemic immune-inflammation index (SII), squamous cell carcinoma antigen (SCC), carbohydrate antigen 125 (CA125) and maximum tumor diameter could serve as a reliable prognostic tool for assessing postoperative recurrence in patients with cervical cancer. Methods: We retrospectively enrolled 186 patients diagnosed with cervical cancer who underwent surgery. The optimal SII cut-off for predicting recurrence was determined as 642.75 by receiver operating characteristic (ROC) analysis; patients were then divided into low-SII and high-SII groups. Pearson correlation analysis assessed multicollinearity among variables. Logistic regression identified independent predictors of recurrence, and ROC curves evaluated the predictive performance of single markers and their combination. Based on the independent predictors identified from multivariate analysis, a nomogram was constructed and internally validated using 500 bootstrap resamples with calibration curves. For external validation, an independent cohort of 103 patients from the same institution between January and December 2025 was enrolled, with the same inclusion and exclusion criteria applied and no overlap of participants between the two cohorts. Results: Following SII-based stratification, patients with higher SII values exhibited more advanced tumor stage, deeper stromal invasion, and higher rates of vascular invasion, perineural invasion, and lymph node metastasis (all $P < 0.05$). All correlation coefficients were < 0.7 , indicating no significant multicollinearity. Multivariate logistic regression identified preoperative SII ($P = 0.015$), SCC ($P = 0.028$), and tumor size ($P = 0.013$) as independent predictors of recurrence. A nomogram incorporating these three predictors was constructed, demonstrating excellent discrimination with an AUC of 0.973 (95% confidence interval [CI]: 0.947-0.999) and good calibration. Internal validation using 500 bootstrap resamples yielded a corrected AUC of 0.969 with an optimism of 0.004 and a mean absolute error of 0.015. External validation in an independent cohort ($n = 103$) achieved an AUC of 0.945 (95% CI: 0.898-0.992) with satisfactory calibration, confirming the nomogram's generalizability and clinical utility. Conclusion: Our analysis confirmed preoperative SII, SCC, and tumor size as independent predictors of postoperative recurrence, with SCC exerting the greatest influence. A nomogram incorporating these three markers was established, demonstrating good discrimination and satisfactory calibration. Internal and external validation collectively confirmed its robustness, supporting its potential for routine clinical assessment of recurrence risk.

Keywords: Cervical cancer, risk of postoperative recurrence, preoperative systemic immune-inflammation index (SII), squamous cell carcinoma antigen (SCC), carbohydrate antigen 125 (CA125), maximum tumor diameter

Introduction

Around the world, cervical cancer remains a prevalent malignancy and a major health threat to women worldwide. For patients receiving surgical treatment, tumor recurrence and metastasis remain the primary obstacles to long-term survival [1-3]. Therefore, it is clinically important to preoperatively identify patients at high risk of recurrence and to develop practical risk assessment tools. These efforts can help clinicians

deliver tailored treatment plans and optimize patient prognosis [2, 4, 5].

The systemic immune-inflammation index (SII), calculated from routine blood counts of neutrophils, platelets, and lymphocytes, is a novel biomarker. It serves as a comprehensive indicator of the body's inflammatory and immune status. Numerous studies have demonstrated that this index is strongly associated with tumor invasion, lymph node metastasis and unfavorable

prognosis in various solid cancers [3, 6, 7]. In patients with cervical cancer, a high SII value is closely related to late International Federation of Gynecology and Obstetrics (FIGO) stage, deep stromal invasion, vascular invasion and lymph node metastasis [4, 7, 8]. Squamous cell carcinoma antigen (SCC) is a classic biomarker commonly used for auxiliary diagnosis and recurrence surveillance of cervical cancer. Nevertheless, using SCC alone cannot achieve satisfactory predictive performance [5, 9-11].

Currently, relevant research on the joint application of preoperative SII and SCC to assess postoperative recurrence risk in cervical cancer remains scarce. Our retrospective study included 186 surgically treated cervical cancer cases. We analyzed how SII relates to various clinicopathological features, determined independent risk factors for recurrence, and finally established and validated a targeted nomogram. The ultimate goal is to provide a useful reference for preoperative risk grouping and personalized treatment of cervical cancer patients [6-14].

Materials and methods

Study subjects

This retrospective study included 186 cervical cancer patients who underwent surgical treatment at The Third Affiliated Hospital of Zunyi Medical University between January 2022 and December 2024. For external validation, an independent cohort of 103 patients who underwent surgery at the same institution between January 2025 and December 2025 was enrolled. The same inclusion and exclusion criteria were applied, and there was no overlap of participants between the two cohorts. All patients were staged according to the FIGO system. Clinical data, including age, histological type, clinical prognostic grouping, degree of differentiation, depth of stromal invasion, vascular invasion, perineural invasion, and recurrence status, were collected from medical records. This study was approved by the ethics committee of The First People's Hospital of Zunyi (The Third Affiliated Hospital of Zunyi Medical University) (No: 2026-1-649).

Inclusion criteria: (1) Complete clinical data; (2) Patients who underwent postoperative follow-up; (3) Patients who adhered to medical advice

and underwent regular postoperative check-ups.

Exclusion criteria: (1) Patients who received neoadjuvant radiotherapy or chemotherapy; (2) Patients with concurrent malignant tumors; (3) Patients with acute or chronic infectious diseases within 2 weeks prior to blood sampling; (4) Patients with autoimmune diseases or those receiving immunosuppressive therapy, including systemic corticosteroids; (5) Patients with hematological disorders affecting peripheral blood cell counts; (6) Patients with incomplete clinical data or lost to follow-up.

After reviewing the medical records of all 186 enrolled patients, none had documented evidence of preoperative infections, autoimmune diseases, corticosteroid use, or hematological disorders affecting blood cell counts within 2 weeks prior to surgery.

Data collection

Peripheral venous blood was collected preoperatively. Neutrophil, platelet, and lymphocyte counts were obtained from routine blood tests, and the SII was calculated as: $SII = \text{platelet count} \times \text{neutrophil count} / \text{lymphocyte count}$.

Fasting peripheral venous blood was collected preoperatively into coagulation-promoting tubes. After centrifugation to separate the serum, serum SCC and carbohydrate antigen 125 (CA125) levels were measured using electrochemiluminescence immunoassay (ECLIA, Roche automated analyzer). Original manufacturer reagents, calibrators, and controls were used according to the kit instructions and clinical laboratory operating procedures. Test data were recorded only after intra-batch quality control results fell within the allowable error range.

Maximum tumor diameter and Ki-67 index were extracted by pathologists from postoperative paraffin-embedded gross specimens and immunohistochemical reports.

Statistical analysis

Statistical analyses were completed via SPSS 27.0 (IBM Corp., Chicago, IL, USA). Normally distributed quantitative data are presented as mean $\pm$ standard deviation, and non-normal data are shown as median and interquartile range. We used independent samples t-test or

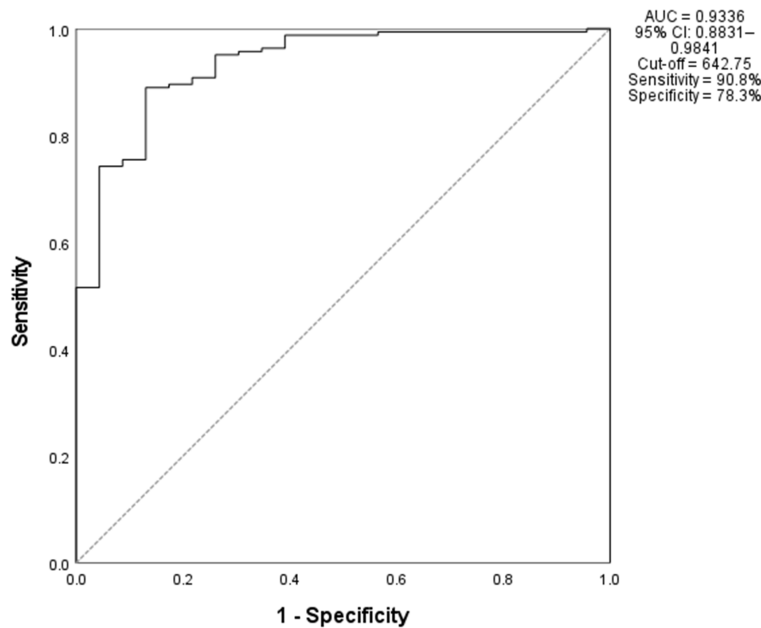


Figure 1. ROC curve of preoperative SII for patient grouping (cutoff 642.75). Note: The receiver operating characteristic (ROC) curve demonstrated that preoperative SII demonstrated favorable predictive efficacy for postoperative recurrence of cervical cancer (AUC = 0.9336, optimal cut-off value = 642.75, sensitivity = 90.8%, specificity = 78.3%). This cutoff value was used for grouping patients into low-SII and high-SII subgroups.

well matched to the baseline recurrence characteristics of the external validation cohort. The recalibrated model was then validated in the independent cohort of 103 patients. We utilized ROC curves and calibration plots to evaluate its predictive discrimination and calibration performance. Decision curve analysis (DCA) was performed to evaluate the clinical net benefit of the nomogram across a range of threshold probabilities (0-100%). DCA calculates the net benefit by weighting true positives and false positives according to the threshold probability, allowing comparison of the nomogram against “treat all” and “treat none” strategies. All statistical analyses in this study were two-tailed, and a *P*-value below 0.05 was defined as statistically significant.

Mann-Whitney U test for between-group comparisons of quantitative indicators, determined by data distribution. Categorical data were recorded as counts and percentages, and analyzed with the χ^2 test or Fisher’s exact test.

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value of SII. Next, Pearson correlation tests were carried out to examine the correlations between all study variables. We then ran univariate and binary logistic regression to screen out factors linked to postoperative recurrence.

Using R 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria), we constructed a nomogram based on the results of multivariate logistic regression. Bootstrap resampling with 500 repetitions was performed for internal validation, and calibration curves were plotted to assess how well the model matched actual outcomes. To account for the difference in overall recurrence rate between the development (2022-2024) and external validation (2025) cohorts, we recalibrated the intercept of the original model. After intercept adjustment, the model’s predicted risk values were

To assess the robustness of the SII cut-off value derived from the Youden index, we performed sensitivity analyses using two alternative threshold selection strategies: (a) the 75th percentile of the SII distribution in the overall cohort; and (b) a clinically rounded threshold of 600, which approximates the Youden-derived cut-off and facilitates clinical interpretation. For each alternative cut-off, we re-ran the multivariate logistic regression model and recalculated the model’s area under the curve (AUC) to evaluate whether SII remained a significant independent predictor and whether model performance was materially affected. Complete separation was diagnosed when the maximum likelihood estimate failed to converge with an abnormally large standard error (> 1,000).

Results

ROC curve of preoperative SII for predicting recurrence

We adopted ROC analysis to examine the prognostic value of preoperative SII for tumor relapse. The AUC reached 0.9336 (95% CI: 0.8831-0.9841, *P* < 0.001), indicating its favor-

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Table 1. Comparison of baseline clinicopathological characteristics between the low-SII group and high-SII group (n = 186)

Variable	Total population (n = 186)	Low SII group (n = 33)	High SII group (n = 153)	P-value	Test statistic
Age (years), $\bar{x} \pm s$	56.9 $\pm$ 11.5	54.2 $\pm$ 10.5	57.5 $\pm$ 11.7	0.131	t = 1.518
Histological type, n (%)				< 0.001	$\chi^2 = 38.751$
Squamous cell carcinoma	160 (86.0)	21 (63.6)	139 (90.8)		
Adenocarcinoma	9 (4.8)	1 (3.0)	8 (5.2)		
Adenosquamous carcinoma	3 (1.6)	0 (0.0)	3 (2.0)		
Other/special type	14 (7.5)	11 (33.3)	3 (2.0)		
FIGO stage, n (%)				0.014	$\chi^2 = 14.233$
Stage IA	43 (23.1)	14 (42.4)	29 (19.0)		
Stage IB	107 (57.5)	19 (57.6)	88 (57.5)		
Stage $\geq$ II	36 (19.4)	0 (0.0)	36 (23.5)		
Degree of differentiation, n (%)				0.057	$\chi^2 = 5.974$
Well differentiated	25 (13.4)	8 (24.2)	17 (11.1)		
Moderately differentiated	150 (80.6)	25 (75.8)	125 (81.7)		
Poorly differentiated	11 (5.9)	0 (0.0)	11 (7.2)		
Depth of stromal invasion, n (%)				< 0.001	$\chi^2 = 45.588$
< 1/2 stroma	68 (36.6)	29 (87.9)	39 (25.5)		
> 1/2 stroma	78 (41.9)	3 (9.1)	75 (49.0)		
Full-layer invasion	40 (21.5)	1 (3.0)	39 (25.5)		
Lymphovascular invasion, n (%)				< 0.001	$\chi^2 = 27.017$
Negative	77 (41.4)	27 (81.8)	50 (32.7)		
Positive	109 (58.6)	6 (18.2)	103 (67.3)		
Perineural invasion, n (%)				< 0.001	$\chi^2 = 22.346$
Negative	106 (57.0)	31 (93.9)	75 (49.0)		
Positive	80 (43.0)	2 (6.1)	78 (51.0)		
Lymph node metastasis, n (%)				0.003	$\chi^2 = 8.974$
Negative	152 (81.7)	33 (100.0)	119 (77.8)		
Positive	34 (18.3)	0 (0.0)	34 (22.2)		
Clinical prognostic group, n (%)				0.010	$\chi^2 = 9.628$
Early stage	150 (80.6)	33 (100.0)	117 (76.5)		
Middle stage	12 (6.5)	0 (0.0)	12 (7.8)		
Advanced stage	24 (12.9)	0 (0.0)	24 (15.7)		

Note: Normally distributed quantitative data were expressed as mean $\pm$ standard deviation, and categorical data were presented as number of cases (percentage). Intergroup comparisons were performed using independent-samples t test, χ^2 test or Fisher's exact test. To avoid low theoretical frequencies, FIGO stage IIA and above were combined into stage $\geq$ II, and rare pathological subtypes were categorized as other/special types. SII: systemic immune-inflammation index; FIGO: International Federation of Gynecology and Obstetrics. Test statistic: t value from independent-samples t-test; χ^2 value from Pearson chi-square test. Fisher's exact test was used for pathological type, degree of differentiation, and clinical prognostic group due to expected cell counts < 5 in some cells; Pearson χ^2 values are reported for reference.

able predictive performance. The Youden index identified 642.75 as the best cut-off value. At this level, the sensitivity was 90.8% and the specificity was 78.3% (**Figure 1**).

Sensitivity analysis for SII cut-off selection

To examine whether the marked sample imbalance (low-SII: n = 33; high-SII: n = 153) influ-

enced our findings, we performed sensitivity analyses using alternative cut-off strategies (**Table 5**). Using the 75th percentile of the SII distribution as the cut-off (SII = 1409.61), the cohort was divided into 140 low-SII and 46 high-SII patients. However, complete separation occurred in the multivariate logistic regression model, resulting in an abnormally large standard error for the SII coefficient (SE =

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Table 2. Comparison of core predictive indicators between the low SII group and high SII group

Indicator	Low SII group (n = 33)	High SII group (n = 153)	Test statistic	P-value
Maximum tumor diameter (cm)	1.00 (0.30, 2.00)	3.20 (2.00, 4.00)	Z = 6.002	< 0.001
Preoperative SCC (ng/mL)	1.00 (0.75, 1.25)	2.70 (1.20, 8.10)	Z = 5.113	< 0.001
Preoperative CA125 (U/mL)	11.00 (8.25, 16.50)	14.40 (9.30, 23.75)	Z = 1.948	0.051
Preoperative SII	561.00 (509.50, 589.35)	1148.00 (859.18, 1494.78)	Z = 9.000	< 0.001
Ki-67 index (%)	60.00 (40.00, 70.00)	61.00 (55.00, 70.00)	Z = 1.396	0.163

Note: Skewed quantitative data were expressed as median (interquartile range), and intergroup comparisons were performed using Mann-Whitney U test. SCC: squamous cell carcinoma antigen; CA125: carbohydrate antigen 125; SII: systemic immune-inflammation index; Ki-67: Ki-67 proliferation antigen. Test statistic: Z value from Mann-Whitney U test.

Table 3. Univariate analysis of risk factors for postoperative recurrence in patients with cervical cancer

Variable	Non-recurrence group (n = 23)	Recurrence group (n = 163)	Test statistic	P value
Measurement data, M (P25, P75)				
Age (years)	52.00 (44.00, 57.00)	58.00 (50.00, 66.00)	Z = 2.614	0.009
Maximum tumor diameter (cm)	0.50 (0.20, 1.50)	3.00 (2.00, 4.00)	Z = 6.558	< 0.001
Preoperative SCC (ng/mL)	1.00 (0.70, 1.10)	2.50 (1.10, 7.70)	Z = 5.141	< 0.001
Preoperative CA125 (U/mL)	11.40 (8.80, 15.00)	14.40 (9.10, 23.10)	Z = 1.686	0.092
Preoperative SII	550.2 (499.1, 640.5)	1120 (817.5, 1473.3)	Z = 6.725	< 0.001
Ki-67 index (%)	40 (30, 60)	65 (55, 70)	Z = 4.405	< 0.001
Enumeration data, n (%)				
Histopathological type			$\chi^2 = 14.152$	0.003
Squamous cell carcinoma	17 (73.9)	143 (87.7)		
Adenocarcinoma	0 (0.0)	9 (5.5)		
Adenosquamous carcinoma	0 (0.0)	3 (1.8)		
Other special types	6 (26.1)	8 (4.9)		
Standard FIGO stage			$\chi^2 = 18.647$	0.002
Stage IA	13 (56.5)	30 (18.4)		
Stage IB	10 (43.5)	97 (59.5)		
Stage IIA	0 (0.0)	10 (6.1)		
Stage IIB	0 (0.0)	2 (1.2)		
Stage III	0 (0.0)	21 (12.9)		
Stage IV	0 (0.0)	3 (1.8)		
Histological differentiation			11.221	0.004
Well-differentiated	8 (34.8)	17 (10.4)		
Moderately differentiated	15 (65.2)	135 (82.8)		
Poorly differentiated	0 (0.0)	11 (6.7)		
Depth of stromal invasion			$\chi^2 = 39.555$	< 0.001
Less than 1/2 layer	22 (95.7)	46 (28.2)		
More than 1/2 layer	1 (4.3)	77 (47.2)		
Full-layer invasion	0 (0.0)	40 (24.5)		
Vascular invasion			$\chi^2 = 37.153$	< 0.001
Negative	23 (100.0)	54 (33.1)		
Positive	0 (0.0)	109 (66.9)		
Perineural invasion			$\chi^2 = 19.808$	< 0.001
Negative	23 (100.0)	83 (50.9)		
Positive	0 (0.0)	80 (49.1)		

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Lymph node metastasis			$\chi^2 = 5.871^*$	0.015
Negative	23 (100.0)	129 (79.1)		
Positive	0 (0.0)	34 (20.9)		
Abnormal SCC			$\chi^2 = 36.340$	< 0.001
Normal	23 (100.0)	55 (33.7)		
Abnormal	0 (0.0)	108 (66.3)		
Abnormal CA125			$\chi^2 = 1.408^*$	0.235
Normal	22 (95.7)	142 (87.1)		
Abnormal	1 (4.3)	21 (12.9)		
Clinical prognostic grouping			$\chi^2 = 6.299^*$	0.043
Early stage	23 (100.0)	127 (77.9)		
Middle stage	0 (0.0)	12 (7.4)		
Advanced stage	0 (0.0)	24 (14.7)		

Note: Quantitative data were presented as median (interquartile range), and intergroup comparisons were performed with Mann-Whitney U test; categorical data were expressed as number of cases (percentage), and intergroup comparisons were conducted using χ^2 test or Fisher's exact test. Test statistic: Z value from Mann-Whitney U test for continuous variables; χ^2 value from Pearson chi-square test for categorical variables. For variables with expected cell counts < 5, *Fisher's exact test was used and P values are reported in the original analysis for reference.

Table 4. Multivariate Logistic regression analysis of influencing factors for postoperative recurrence in cervical cancer patients

Variable	β	S.E.	Wald χ^2	df	P value	OR	95% CI
Preoperative SII	0.007	0.003	5.958	1	0.015	1.007	1.001-1.012
Preoperative SCC (ng/mL)	1.949	0.889	4.807	1	0.028	7.023	1.230-40.118
Preoperative CA125 (U/mL)	-0.010	0.027	0.124	1	0.725	0.990	0.939-1.045
Maximum tumor diameter (cm)	1.673	0.675	6.139	1	0.013	5.330	1.419-20.024
FIGO stage (reference: stage IA)							
Non-stage IA	-0.605	1.034	0.342	1	0.558	0.546	0.072-4.143

Note: β = regression coefficient; S.E. = standard error; Wald χ^2 = Wald chi-square statistic; df = degrees of freedom; OR = odds ratio; CI = confidence interval. Binary logistic regression with the enter method was used; FIGO stage IA was set as the reference group.

Table 5. Sensitivity analysis of different SII cut-off values for predicting postoperative recurrence

Cut-off strategy	Cut-off value	Low-SII (n)	High-SII (n)	SII OR (95% CI)	SII P-value	AUC (95% CI)
Youden index	642.75	33	153	1.007 (1.001-1.012)	0.015	0.973 (0.947-0.999)
75th percentile	1409.61	140	46	NE	NE	NE
Clinical threshold	600	26	160	23.948 (4.34-132.2)	< 0.001	0.982

Note: NE = Not estimable due to complete separation. AUC, area under the curve; CI, confidence interval; OR, odds ratio; SII, systemic immune-inflammation index.

2,995.6) and an unreliable P-value (0.996), suggesting that this threshold too perfectly separated recurrence outcomes to allow stable estimation. Using a clinically rounded threshold of 600 (SII $\geq$ 600 vs. < 600), the cohort was divided into 26 low-SII and 160 high-SII patients. SII remained a highly significant independent predictor (OR = 23.948, 95% CI: 4.34-132.2, $P < 0.001$), and the model maintained excellent discrimination (AUC = 0.982). Collectively, these sensitivity analyses confirm that

the predictive value of SII is robust to the choice of cut-off, despite the sample imbalance observed with the Youden index-derived threshold.

Baseline characteristics of the study population

Based on the optimal preoperative SII cut-off, the 186 patients were divided into low-SII (n = 33) and the high-SII (n = 153) groups. We then

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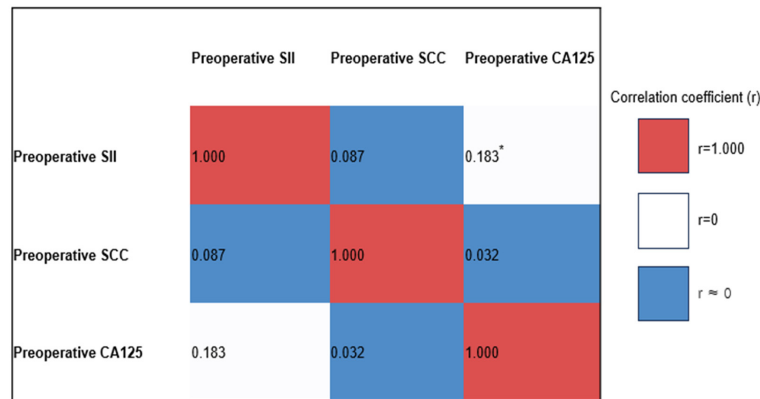


Figure 2. Correlation heatmap of preoperative SII, SCC, and carbohydrate antigen 125 (CA125). Note: Pearson correlation analysis was performed. The color blocks represent the correlation coefficient (r) between variables. Red indicates strong positive correlation, while blue and white indicate weak or no correlation. * $P < 0.05$ indicates a statistically significant correlation.

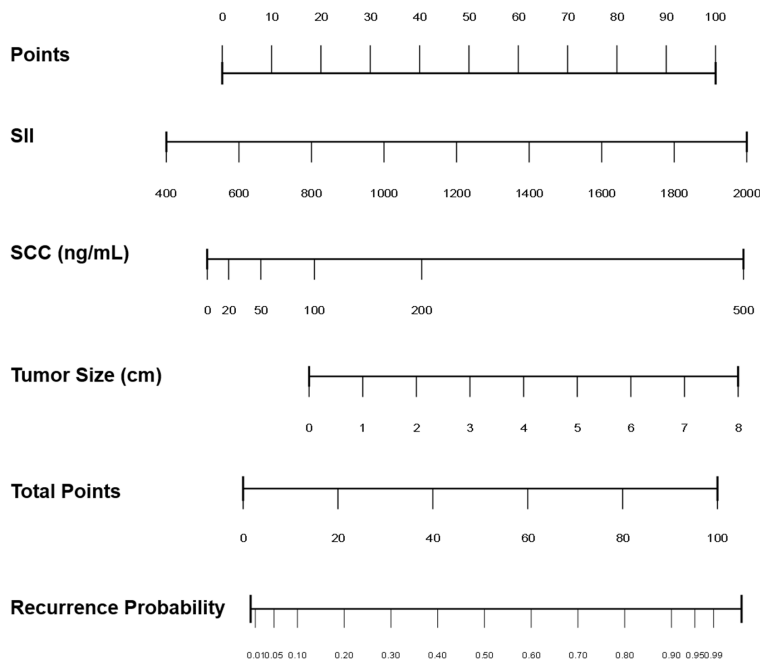


Figure 3. Nomogram for predicting the risk of postoperative recurrence of cervical cancer. Note: The nomogram incorporates three independent predictors: preoperative systemic immune-inflammatory index (SII), squamous cell carcinoma antigen (SCC), and tumor size. Each variable is assigned a score according to its contribution to recurrence risk. The sum of the scores (Total Points) corresponds to the predicted recurrence probability at the bottom axis.

compared the two groups across multiple baseline clinicopathological features, such as age, histological type, FIGO stage, tumor differentiation, stromal invasion depth, vascular invasion, perineural invasion, lymph node metastasis

and clinical risk stratification. No significant intergroup differences were observed for age and tumor differentiation (both $P > 0.05$), whereas all other examined variables differed significantly ($P < 0.05$) (**Table 1**).

Comparison of core predictive indicators

Core predictive indicators, including maximum tumor diameter, preoperative SCC, preoperative CA125, preoperative SII, and Ki-67 index, were compared between the low-SII and high-SII groups. Significant differences were observed in maximum tumor diameter, preoperative SCC, preoperative CA125, and preoperative SII (all $P < 0.05$), while the difference in Ki-67 index was not statistically significant ($P > 0.05$) (**Table 2**).

Correlation heatmap

Pearson correlation analysis was performed on preoperative SII, SCC, and CA125. The results showed a weak positive correlation between SII and CA125 ($r = 0.183$, $P < 0.05$), while no significant correlations were observed between SII and SCC or between SCC and CA125 ($P > 0.05$). The absolute values of all correlation coefficients were less than 0.7, indicating the absence of strong collinearity among the variables and supporting their inclusion in the multivariate regression model (**Figure 2**).

Univariate analysis of risk factors for postoperative recurrence

Univariate logistic regression analysis identified age, maximum tumor diameter, preopera-

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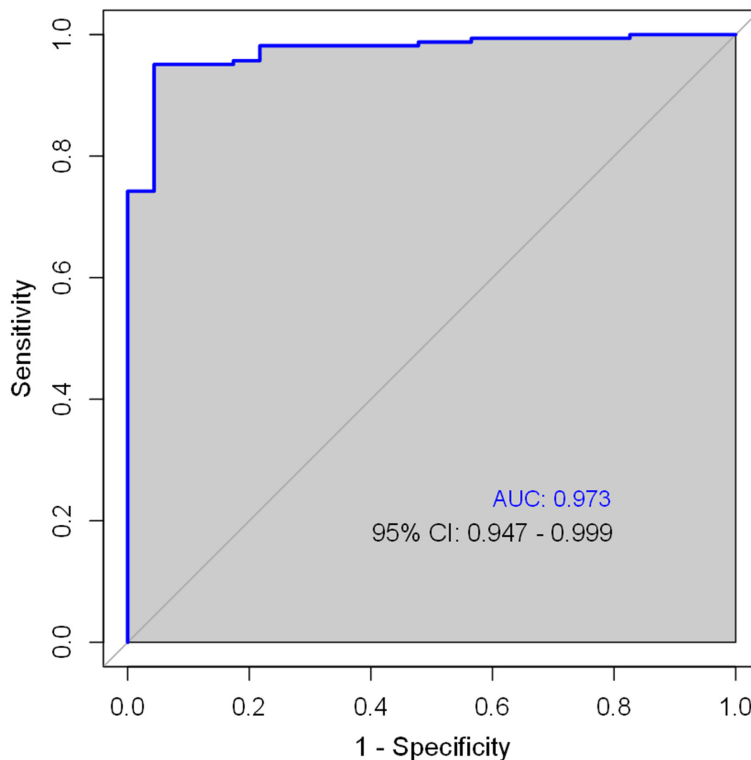


Figure 4. Receiver operating characteristic (ROC) curve of the nomogram for predicting postoperative recurrence.

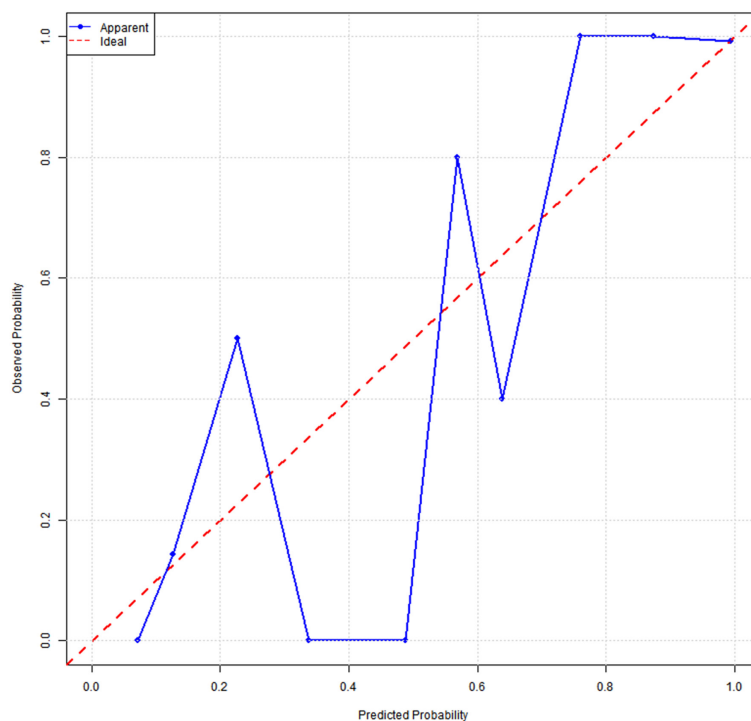


Figure 5. Calibration curve of the nomogram. Note: Apparent calibration curve of the nomogram in the training cohort. The blue solid line indicates the observed recurrence probability, and the red dashed line represents the ideal calibration line. The calibration curve closely approximates the ideal line, with only minor deviations in certain intervals.

tive SCC, preoperative SII, Ki-67 index, histological type, FIGO stage, degree of differentiation, depth of stromal invasion, vascular invasion, perineural invasion, lymph node metastasis, and abnormal SCC status as significant predictors of recurrence (all $P < 0.05$). In contrast, preoperative CA125 level and abnormal CA125 status were not significantly associated ($P > 0.05$). All variables with $P < 0.2$ were included in the multivariate logistic regression model for further analysis (**Table 3**).

Independent risk factors associated with cervical cancer postoperative recurrence: a multivariate logistic regression analysis

Variables eligible for multivariate regression were chosen based on two considerations: univariate results with $P < 0.20$, as well as the research objective and clinical significance. The selected items included preoperative SII, SCC, CA125, maximum tumor diameter, FIGO stage, vascular invasion and lymph node metastasis.

Multivariate logistic regression identified preoperative SII, SCC, and maximum tumor diameter as independent predictors of postoperative recurrence (all $P < 0.05$). SCC exerted the greatest effect (odds ratio [OR] = 7.023), while SII had a relatively modest impact (OR = 1.007). Specifically, each one-unit increase in SII was associated with a 0.7% increase in recurrence risk, and each 1 cm increase in tumor size conferred a more pronounced elevation in risk (OR = 5.330). These results indicate that the joint

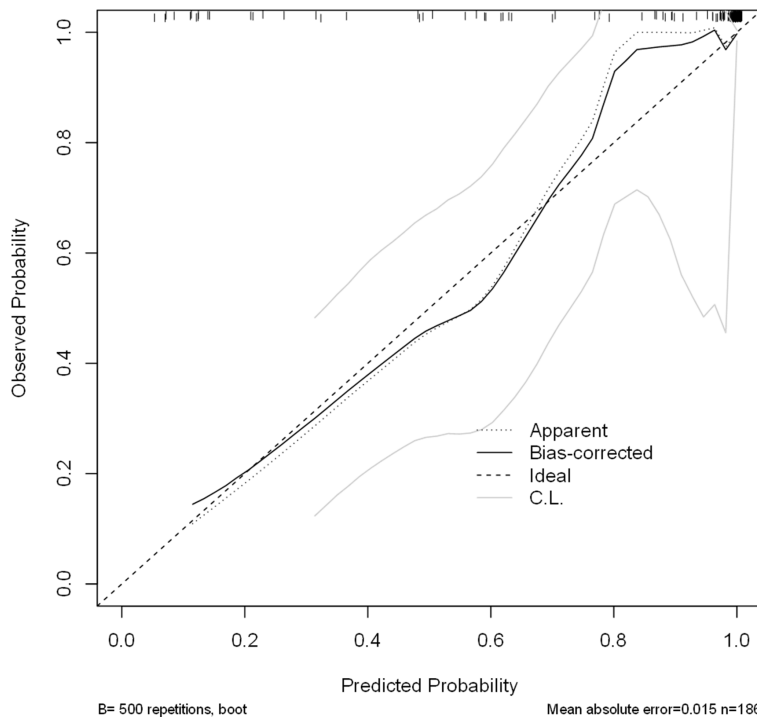


Figure 6. Bootstrap internal validation calibration curve. Note: The top curve is the apparent curve, the middle curve is the bias-corrected curve, and the bottom dashed curve is the ideal curve. The bias-corrected curve closely approximates the ideal curve, with a mean absolute error of 0.015 and a bias-corrected AUC of 0.969 ($n = 186$).

detection of preoperative SII and SCC is useful for judging postoperative recurrence risk (Table 4).

Construction of the nomogram

Using the independent predictors screened via multivariate logistic regression, we developed a nomogram to forecast postoperative recurrence risk in cervical cancer. Preoperative SII, SCC and maximum tumor diameter were integrated into this model. Every indicator was given a score proportional to its impact on recurrence. The total score can then be matched to the corresponding recurrence probability on the horizontal axis at the bottom (Figure 3).

ROC curve of the nomogram for predicting postoperative recurrence

ROC testing for the nomogram gave an AUC of 0.973 (95% CI: 0.947-0.999). The nomogram stratifies patients according to their recurrence risk (Figure 4).

Calibration of the nomogram

Calibration curves are used to assess the agreement between the predicted probabilities from the nomogram and the actual observed probabilities. The ideal calibration reference is indicated by the red dashed line, with the blue line depicting the observed calibration curve. Within the high-risk range, the observed curve tracks the reference line tightly. Furthermore, the low-risk interval exhibits no evidence of systematic deviation (Figure 5).

Internal validation

To complete internal validation for the nomogram, we ran Bootstrap resampling for 500 times. Relevant calibration plots are presented in Figure 6. Little deviation existed between the bias-corrected curve and the ideal curve, with a mean absolute error

of 0.015. Calculations returned a corrected C-index of 0.969 and an optimism value of 0.004. The above outcomes prove the model is stable and well-calibrated, without apparent overfitting issues.

External validation

For external validation, we tested the intercept-corrected nomogram in an independent cohort of 103 patients from the same institution (January 2025 to December 2025). This cohort comprised 31 confirmed recurrence cases (30.1%). There was no participant overlap with the group used for model construction. ROC analysis gave an AUC of 0.945 (95% CI: 0.898-0.992). It proves the nomogram still delivers strong discriminative ability and good applicability across different patient groups. See Figure 7 for details.

External validation calibration curve

The initial model overestimated risks for external participants. Intercept correction fixed this

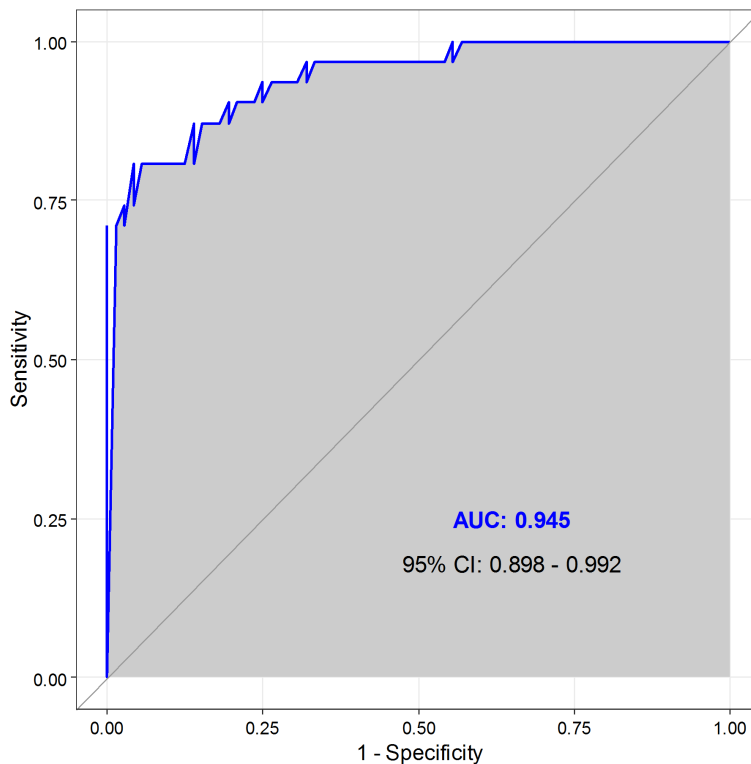


Figure 7. External validation receiver operating characteristic (ROC) curve. Note: Sensitivity: True Positive Rate; 1 - Specificity: False Positive Rate. The grey diagonal line represents random prediction. The blue curve is the receiver operating characteristic (ROC) curve of the calibrated nomogram in the external validation cohort (area under the curve [AUC] = 0.945).

issue and brought predicted values in line with real recurrence rates. As shown in **Figure 8**, the two curves fit closely, proving the model's predictions are consistent with actual findings.

Decision curve analysis

Decision curve analysis was performed to evaluate the clinical utility of the nomogram (**Figure 9**). The DCA demonstrated that the nomogram provided superior net benefit compared with the “treat all” and “treat none” strategies across a broad range of clinically meaningful threshold probabilities, confirming its clinical applicability for postoperative risk stratification.

Discussion

In our cohort, preoperative SII levels increased with disease progression. Higher SII was associated with deeper stromal invasion and a greater likelihood of vascular invasion, perineural invasion, and lymph node metastasis.

Correlation tests confirmed no significant collinearity between SII and SCC, supporting their combined use for risk prediction.

SII is calculated as platelet count $\times$ neutrophil count/lymphocyte count, and each component contributes distinct biological functions in cervical cancer progression. Neutrophils promote tumor invasion through the secretion of neutrophil elastase and matrix metalloproteinases, which degrade extracellular matrix and facilitate epithelial-mesenchymal transition [15]. Additionally, neutrophil extracellular traps (NETs) have been shown to awaken dormant cancer cells and promote metastatic recurrence [16]. Platelets protect circulating tumor cells from immune surveillance by forming physical cloaks and releasing transforming growth factor- β (TGF- β), which suppresses natural killer cell activity and

promotes metastatic niche formation [17, 18]. Conversely, lymphocytes-particularly CD8⁺ cytotoxic T cells-constitute the primary antitumor effector arm, and their reduction permits immune evasion. Therefore, an elevated SII not only reflects systemic inflammation but also signifies a shift toward a pro-tumorigenic immune landscape, where enhanced tumor invasion and suppressed immune surveillance jointly facilitate recurrence.

The biological rationale for combining SII with SCC lies in their complementary pathways in tumor immune evasion. SCC antigen, a serine protease inhibitor (serpin) belonging to the SERPINB3 family, has been shown to promote an immunosuppressive tumor microenvironment through STAT-dependent chemokine production [19]. Specifically, SCCA1/SERPINB3 upregulates CXCL1/8 and other chemokines that recruit myeloid-derived suppressor cells (MDSCs) and impair CD8⁺ T cell infiltration and function, thereby suppressing antitumor immunity [19]. Notably, this immunosuppres-

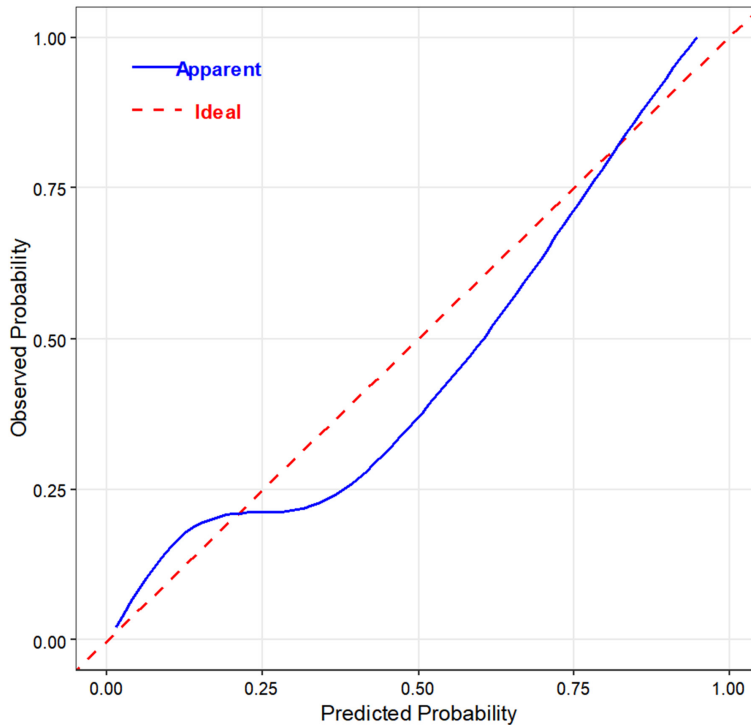


Figure 8. External validation calibration curve. Note: The x-axis represents the calibrated predicted probability, and the y-axis represents the observed probability. The blue solid line represents the actual calibration curve (Apparent), and the red dashed line represents the ideal calibration line (Ideal). This external validation curve was generated after intercept calibration.

sive role of SERPINB3 has been directly demonstrated in cervical cancer, where its expression correlates with reduced T cell activation signatures [19]. In contrast, SII captures the global systemic inflammatory milieu, reflecting the relative abundance of immunosuppressive neutrophils and platelets versus effector lymphocytes. While SCC directly shapes the local immune microenvironment through tumor-secreted factors, SII indicates the host's broader immune-inflammatory balance. These two biomarkers therefore capture orthogonal yet synergistic dimensions of the tumor-immune ecosystem—one reflecting local immune suppression mediated by tumor-derived SERPINB3, the other indicating the host's systemic inflammatory status—providing a more comprehensive risk assessment than either marker alone.

Univariate and multivariate logistic regression identified preoperative SII, SCC, and maximum tumor diameter as independent predictors of postoperative recurrence (**Table 4**). Among these, SCC demonstrated the strongest effect

(OR = 7.023), followed by tumor size (OR = 5.330 per 1 cm increase), while SII as a continuous variable showed a modest effect (OR = 1.007 per unit increment). However, when SII was categorized using clinically meaningful thresholds, its predictive value became more clinically interpretable: patients with SII $\geq$ 600 had a substantially higher recurrence risk (OR = 23.948, $P < 0.001$; **Table 5**), confirming that the clinical utility of SII lies in risk stratification rather than per-unit interpretation. These findings are consistent with previous studies demonstrating the prognostic value of inflammatory markers in cervical cancer [4, 10, 14, 20-30].

Based on the independent predictors identified, we developed a nomogram for individual recurrence risk assessment. The model demonstrated excellent discrimination in the training cohort (AUC = 0.973) and maintained strong performance in internal validation (bootstrap-corrected AUC = 0.969) and external validation (AUC = 0.945). Calibration curves showed good agreement between predicted and observed outcomes, confirming the model's generalizability.

The nomogram combined SII, SCC, and maximum tumor diameter for risk prediction. This combined approach demonstrated superior predictive performance compared with any single indicator. This finding may assist clinicians in developing personalized treatment strategies and optimizing postoperative follow-up schedules [16, 31-33]. All indicators adopted in this model come from routine clinical tests. As this model relies on routine, non-invasive laboratory tests, it is cost-effective and readily applicable in clinical practice. The DCA results further support the clinical utility of the nomogram (**Figure 9**). The observation that the nomogram provided superior net benefit over both extreme strategies suggests that clinicians can use this tool to guide postoperative

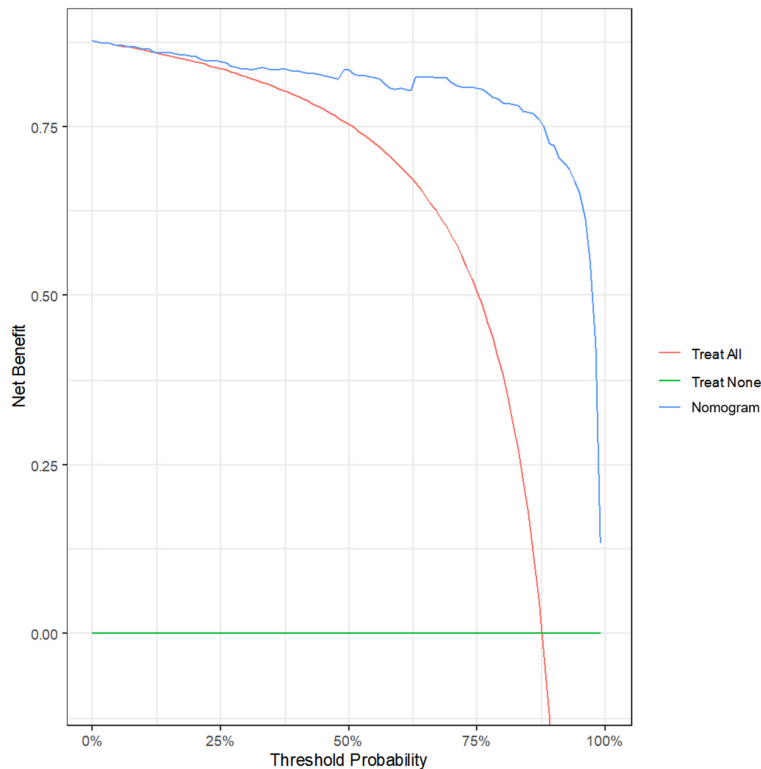


Figure 9. Decision curve analysis (DCA) of the nomogram. Note: The x-axis represents the threshold probability, and the y-axis represents the net benefit. The blue curve represents the nomogram. The red/orange curve represents the “treat all” strategy, and the green horizontal line at $y = 0$ represents the “treat none” strategy. The nomogram demonstrated superior net benefit compared with both extreme strategies across the entire range of threshold probabilities.

management decisions, regardless of individual risk tolerance levels.

Several limitations of this study should be acknowledged. First, as a single-center retrospective study, selection bias could not be entirely avoided, and the sample size was relatively limited. Second, although SII is presumed to reflect host immune-inflammatory status, we did not directly correlate preoperative SII with intratumoral immune cell infiltration due to the absence of corresponding histological or immunohistochemical data. We acknowledge that whether peripheral blood-derived SII faithfully represents the local tumor micro-environment (TME) remains an open question, as discordance between systemic and local immunity has been documented in various malignancies [34, 35]. Ideally, multiplex immunofluorescence staining for CD3⁺, CD8⁺, CD68⁺, and FoxP3⁺ on archived tissues would

have substantiated the relationship between SII and TME composition; however, tissue availability constraints precluded such analyses in the current study. Consequently, whether SII correlates with intratumoral CD8⁺ T cell infiltration, myeloid-derived suppressor cell accumulation, or other local immune phenotypes remains to be determined. Third, we did not account for postoperative adjuvant therapy, HPV infection status, or dynamic changes in biomarker levels over time in our analysis [11, 21, 36–38]. Fourth, the optimal SII cut-off of 642.75, derived by the Youden index, resulted in substantial sample size imbalance (33 vs. 153). To address this concern, we performed sensitivity analyses using two alternative threshold strategies (Table 5). The 75th percentile cut-off (SII = 1409.61) yielded a more balanced distribution (140 vs. 46) but led to complete separation in the regression model, precluding reliable es-

timation of the odds ratio and P -value. Using a clinically rounded threshold of 600 (SII ≥ 600 vs. < 600 ; 26 vs. 160), SII remained a highly significant independent predictor (OR = 23.948, $P < 0.001$) with excellent model discrimination (AUC = 0.982), confirming the robustness of our findings. Nevertheless, the specific Youden-derived threshold should be cautiously interpreted and validated in larger, independent cohorts before clinical implementation. Fifth, due to the retrospective design, we cannot establish causality between elevated SII and increased recurrence risk, but only an association. Sixth, although we explicitly defined exclusion criteria for preoperative infections, autoimmune diseases, and corticosteroid use, the retrospective nature of this study limited our ability to comprehensively verify all such conditions from medical records. We cannot completely exclude the possibility of subclinical infections or undocument-

ed medication use that might influence SII levels. In the future, we plan to conduct multi-center prospective cohort studies with comprehensive tissue biobanking and systematic immune profiling, which will help further validate and refine the model and strengthen the clinical evidence supporting its routine use.

Conclusion

This study identified preoperative SII, SCC and maximum tumor diameter as three independent risk factors for postoperative recurrence in cervical cancer patients. SCC exhibited the strongest predictive effect, whereas SII showed a relatively modest association (OR = 1.007). A nomogram combining these three parameters was developed to estimate recurrence risk. Its performance was assessed through bootstrap internal validation and external cohort verification. The results demonstrated consistent predictive accuracy and satisfactory calibration, supporting the model's generalizability.

This tool relies solely on routine laboratory data and is non-invasive, facilitating its clinical adoption. However, the single-center, retrospective design may have introduced selection bias and data imbalance. Larger, multicenter prospective studies are warranted to validate its real-world performance and promote routine clinical implementation.

Disclosure of conflict of interest

None.

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