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Article

Diagnostic Value of SCC-Ag Combined With CYFRA 21-1 in Predicting Long-Term Lymph Node Metastasis After Cervical Cancer Surgery

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Abstract

Aims/Background: Lymph node metastasis (LNM) is an important prognostic factor of cervical cancer, significantly impacting patient outcomes and treatment strategies. Current methods for predicting LNM after surgery are limited, necessitating the identification of reliable biomarkers. This study aimed to evaluate the diagnostic value of serum squamous cell carcinoma antigen (SCC-Ag) combined with cytokeratin fragment 21-1 (CYFRA 21-1) for identifying long-term LNM after cervical cancer surgery. **Methods**: A retrospective case-control study was conducted on 138 patients with primary cervical cancer who underwent radical hysterectomy and pelvic lymphadenectomy between May 2020 and May 2023. Patients were followed up for at least two years post-surgery, with a focus on their LNM status. Serum SCC-Ag and CYFRA 21-1 levels were measured using an electrochemiluminescence immunoassay analyzer. Patients were classified into two groups based on the presence of LNM detected during follow-up: without LNM and with LNM groups. The cohort was further divided into a training set ($n = 85$) and a test set ($n = 53$). Univariate and multivariate logistic regression analysis identified significant predictors, which were used to construct a nomogram diagnostic model. Model performance was evaluated using calibration curves, receiver operating characteristic curve analysis, and decision curve analysis. **Results**: Elevated serum SCC-Ag and CYFRA 21-1 levels were observed in patients with LNM compared to those without. Multivariate logistic regression identified both of these markers as independent predictors of long-term LNM (all $p < 0.05$). The constructed nomogram model integrating these markers demonstrated high discriminatory power, with an area under the curve of 0.869 in the training set and 0.861 in the test set. **Conclusion**: Serum SCC-Ag and CYFRA 21-1 levels may serve as valuable biomarkers for predicting long-term LNM after cervical cancer surgery. A nomogram model integrating these markers provides enhanced diagnostic accuracy and could potentially guide personalized treatment strategies.

Keywords: cervical cancer; lymph node metastasis; SCC-Ag; CYFRA 21-1; diagnosis

1. Introduction

Cervical cancer remains a significant global health burden, with approximately 604,000 new cases and 342,000 deaths reported annually [1]. It disproportionately affects women in low- and middle-income countries, where screening programs and access to healthcare may be limited [2]. Despite advancements in prevention through vaccination against human papillomavirus (HPV), cervical cancer continues to pose a substantial risk, particularly among older populations and those infected with high-risk HPV types [3].

The diagnosis of cervical cancer typically involves a combination of cytology (pap smear), HPV testing, colposcopy, and biopsy [4]. Early detection through screening has led to improved outcomes, but challenges remain in identifying patients at high risk for lymph node metastasis (LNM) following surgical treatment. Current diagnostic methods rely heavily on imaging techniques such as pelvic magnetic resonance imaging (MRI) and computed tomography (CT) scans, which can be costly and not always available in resource-limited settings [5].

Treatment strategies for cervical cancer depend on the stage of the disease and patient-specific factors. For early-stage cervical cancer (stages I–IIA, based on international federation of gynecology and obstetrics [FIGO] 2018 criteria [6]: IA, microinvasive carcinoma with stromal invasion $\leq$5 mm in depth; IB, clinically visible lesion confined to the cervix or lesion $>$IA but $\leq$4 cm in size; IIA, tumor invades beyond the cervix to the upper two-thirds of the vagina but not to the parametrium), radical hysterectomy combined with pelvic lymphadenectomy is the standard treatment. Given the presence of LNM significantly impacts prognosis and necessitates adjuvant therapies such as chemotherapy and radiotherapy, identifying reliable biomarkers for predicting LNM can aid in tailoring postoperative management and improving patient outcomes [7,8]. However, current clinical and pathological parameters often fall short in providing reliable prognostic information, necessitating the identification of novel biomarkers that can enhance diagnostic accuracy [9,10].

The role of tumor markers in oncology has been increasingly recognized due to their potential in early diagnosis, prognosis, and therapeutic monitoring. Among these,

squamous cell carcinoma antigen (SCC-Ag) and cytokeratin fragment 21-1 (CYFRA 21-1) have garnered attention for their utility in various malignancies, including cervical cancer. SCC-Ag, a glycoprotein overexpressed in squamous cell carcinomas, has been associated with tumor burden and aggressiveness [11,12]. Elevated levels of SCC-Ag correlate with advanced tumor stages and adverse outcomes, making it a valuable marker for disease progression [13]. CYFRA 21-1, a fragment of cytokeratin 19, is another promising biomarker that reflects epithelial cell turnover and tissue destruction during tumor progression. Studies have shown that elevated CYFRA 21-1 levels are linked to poor prognosis in several cancers, suggesting its potential as a prognostic indicator in these malignancies, including cervical cancer [14–16].

Despite individual contributions of SCC-Ag and CYFRA 21-1 in predicting cervical cancer outcomes, their combined use has not been extensively explored. The rationale behind combining multiple biomarkers lies in their complementary nature, and such a multi-marker approach confers enhanced diagnostic accuracy and provides a more comprehensive risk assessment. Previous studies have demonstrated that integrating multiple tumor markers can improve the detection rate of malignancies and refine prognostic predictions [17,18]. For instance, the combination of cancer antigen 125 (CA125), human epididymis protein 4 (HE4), and mesothelin has been shown to outperform either marker alone in the prognostication of ovarian cancer [19]. Similarly, the integration of SCC-Ag and CYFRA 21-1 may enhance the diagnostic performance for LNM in cervical cancer patients, thereby supporting more personalized treatment strategies.

Moreover, the development of diagnostic models incorporating these biomarkers could significantly impact clinical practice. Such models, often constructed using multivariate logistic regression or machine learning algorithms, aim to integrate multiple factors to provide a holistic risk assessment. By leveraging the strengths of different biomarkers, these models can offer improved discriminatory power compared to traditional clinical and pathological criteria. This approach holds promise for optimizing treatment strategies based on individual patient risk profiles, ultimately leading to better outcomes. Given the complexity of cervical cancer and the variability in patient responses, the need for robust diagnostic tools is paramount. Therefore, investigating the combined diagnostic value of SCC-Ag and CYFRA 21-1 represents a critical step towards advancing personalized medicine in cervical cancer management.

2. Methods

2.1 Study Participants and Selection Criteria

This study is a retrospective case-control study that consecutively enrolled 138 patients with cervical cancer who underwent surgical treatment at the Department of Obstetrics and Gynecology, Shandong Public Health Clinical Center, from May 2020 to May 2023. Inclusion criteria of this study include the following: (1) patients aged between 18 and 75 years; (2) patients diagnosed with primary cervical cancer confirmed with both preoperative cervical biopsy and postoperative pathological examination [20]; (3) patients meeting the international federation of gynecology and obstetrics (FIGO) 2018 staging criteria [6], with stages ranging from IA to IIA; (4) patients who had received initial treatment which encompassed radical hysterectomy and pelvic lymphadenectomy, with or without para-aortic lymphadenectomy, and did not receive adjuvant chemoradiotherapy after surgery; (5) patients who had been tested for serum SCC-Ag and CYFRA 21-1 within one week before surgery, with complete medical records; and (6) patients who had been regularly followed up after surgery for at least two years, with complete follow-up data. Exclusion criteria include: (1) individuals with distant organ metastasis (such as lung, liver, bone metastasis) or pelvic LNM confirmed with preoperative imaging or pathology; (2) pregnant or lactating women; (3) patients with acute pelvic inflammatory disease, autoimmune diseases, or liver or kidney failure; (4) patients with other malignancies or a history of previous malignancy; and (5) patients with a history of neoadjuvant chemotherapy or other treatments prior to surgery.

2.2 Long-Term Follow-Up and Grouping

Based on cervical cancer treatment guidelines [20], patients underwent clinical evaluations every three months during the first two years post-surgery to achieve the optimal balance between effective disease monitoring and the rational utilization of healthcare resources. These evaluations included physical examinations, symptom assessments, and blood tests for tumor markers, with a focus on whether enlarged lymph nodes were palpable in the pelvic and inguinal regions. If any suspicious signs (such as palpable enlarged lymph nodes) were detected during the three-month clinical follow-ups, immediate imaging studies were scheduled for confirmation. Enhanced pelvic magnetic resonance imaging (or computed tomography) was performed every six months, with additional scans of the para-aortic lymph node region indicated if necessary. Suspicious lymph nodes identified through imaging were surgically removed and biopsied to obtain pathological evidence. Excluding lost-to-follow-up and deceased cases, this study ultimately included 138 eligible patients. According to whether regional LNM occurred during the follow-up period, patients were classified into two groups: the without LNM group and the with LNM group. To ensure the randomness and independence of the division between the training set and the test set, and to avoid introducing selection bias, we used a random number sequence generated by SPSS 29.0 software (developed by SPSS Inc., Chicago, IL, USA). The entire patient cohort ($n = 138$) was divided into a

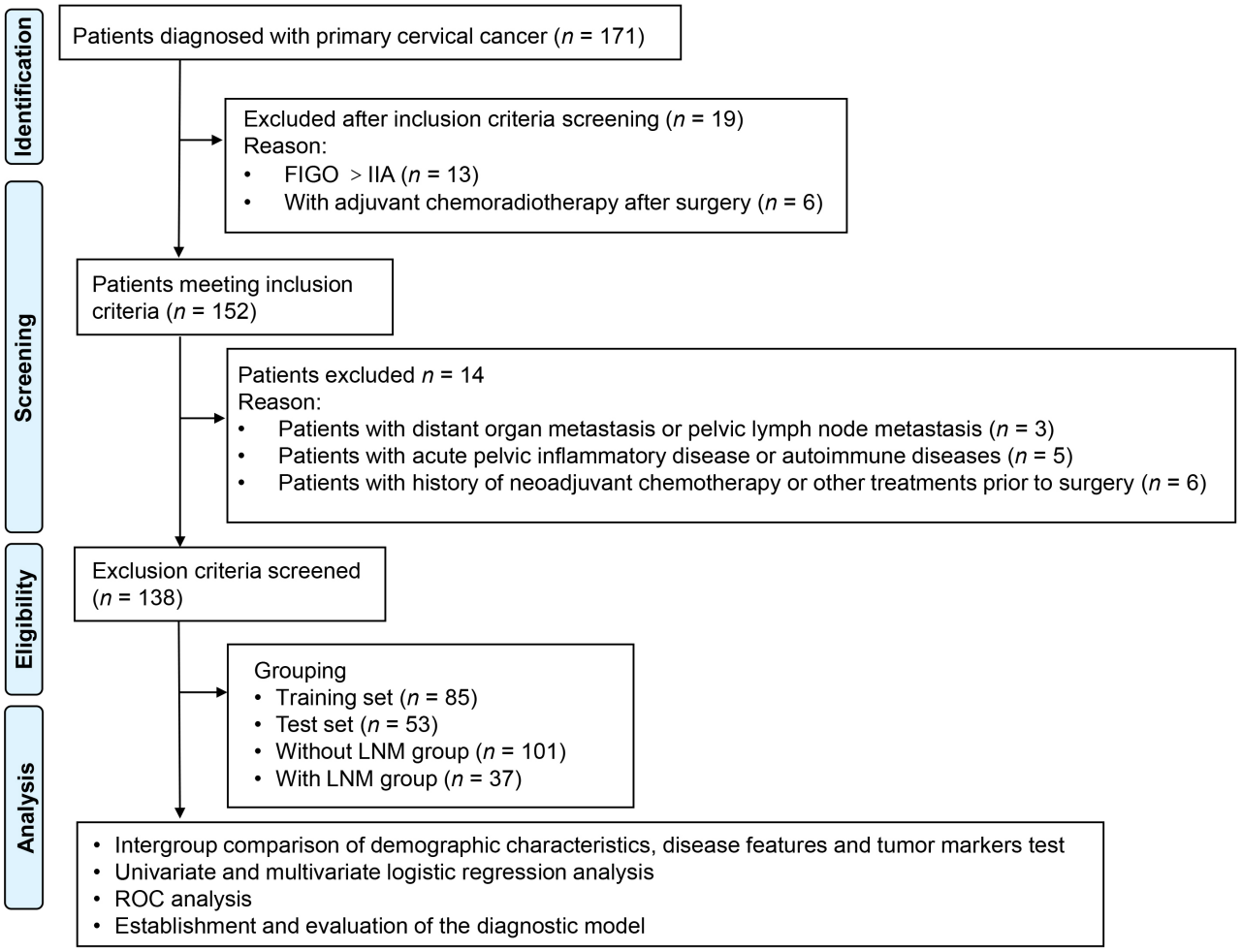

Fig. 1. Flowchart of study participant selection. FIGO staging definitions (based on FIGO 2018 criteria [6]): IIA, tumor invades beyond the cervix to the upper two-thirds of the vagina but not to the parametrium. FIGO, international federation of gynecology and obstetrics; LNM, lymph node metastasis; ROC, receiver operating characteristic.

training set (n = 85) and a test set (n = 53) in an approximate 6:4 ratio using a simple random sampling method. Among them, the training set (n = 85) included 63 patients without LNM and 22 patients with LNM; the test set (n = 53) included 38 patients without LNM and 15 patients with LNM (Fig. 1, Ref. [6]).

This study retrospectively collected demographic characteristics, disease features, and tumor markers of the study participants through the electronic medical record system. Demographic characteristics included age, body mass index (BMI), ethnicity, menopausal status, smoking history, history of hypertension, history of diabetes, and family history of cervical cancer. Disease features encompassed pathological type, FIGO staging, maximum tumor diameter, differentiation degree, appearance type, depth of myometrial invasion, and vascular cancer thrombus status. Tumor markers included preoperative serum levels of SCC-Ag, CYFRA 21-1, CA125, and carcinoembryonic antigen (CEA).

2.3 Measurements of Tumor Markers

Fasting venous blood (3 mL) was collected from every patient before surgery. The blood specimens were centrifuged at 3000 rpm for 10 minutes, and the upper serum layer was separated for the following tests:

(1) Squamous cell carcinoma-related markers: The serum SCC-Ag levels and CYFRA 21-1 levels were measured using a fully automated electrochemiluminescence immunoassay analyzer (cobas e601, Roche Diagnostics, Basel, Switzerland). The normal reference levels were $\leq$1.5 ng/mL for SCC-Ag and $\leq$3.3 ng/mL for CYFRA 21-1.

(2) Adenocarcinoma and mixed-type related markers: The CEA and CA125 were also measured using the aforementioned fully automated electrochemiluminescence immunoassay analyzer. The normal reference ranges were $\leq$5.0 ng/mL for CEA and $\leq$35 U/mL for CA125.

Table 1. Comparison of all data between training set and test set.

Variables	Training set (n = 85)	Test set (n = 53)	t/χ^2	p
LNM, n (%)			0.097	0.755
Without LNM	63 (74.12%)	38 (71.70%)		
With LNM	22 (25.88%)	15 (28.30%)		
Demographic characteristics				
Age (years)	60.47 ± 6.65	60.74 ± 7.12	0.224	0.823
BMI (kg/m^2)	22.50 ± 1.68	22.49 ± 1.68	0.042	0.966
Ethnicity, n (%)			0.307	0.580
Han	79 (92.94%)	47 (88.68%)		
Others	6 (7.06%)	6 (11.32%)		
Menopause, n (%)			0.023	0.880
Yes	47 (55.29%)	30 (56.60%)		
No	38 (44.71%)	23 (43.40%)		
Smoking, n (%)			0.002	0.964
Yes	11 (12.94%)	7 (13.21%)		
No	74 (87.06%)	46 (86.79%)		
Hypertension, n (%)			0.001	0.981
Yes	21 (24.71%)	13 (24.53%)		
No	64 (75.29%)	40 (75.47%)		
Diabetes, n (%)			0.020	0.889
Yes	25 (29.41%)	15 (28.30%)		
No	60 (70.59%)	38 (71.70%)		
Family history of cervical cancer, n (%)			0.023	0.880
Yes	12 (14.12%)	7 (13.21%)		
No	73 (85.88%)	46 (86.79%)		
Disease features				
Pathological type, n (%)			0.331	0.847
Squamous cell carcinoma	75 (88.24%)	45 (84.91%)		
Adenocarcinoma	6 (7.06%)	5 (9.43%)		
Adenosquamous carcinoma	4 (4.71%)	3 (5.66%)		
FIGO staging, n (%)			0.114	0.945
IA	33 (38.82%)	21 (39.62%)		
IB	29 (34.12%)	19 (35.85%)		
IIA	23 (27.06%)	13 (24.53%)		
Tumor diameter (cm)	2.58 ± 0.72	2.63 ± 0.84	0.268	0.789
Degree of differentiation, n (%)			0.203	0.903
Poorly differentiated	40 (47.06%)	27 (50.94%)		
Moderately differentiated	36 (42.35%)	21 (39.62%)		
Highly differentiated	9 (10.59%)	5 (9.43%)		
Appearance type, n (%)			0.324	0.955
Exophytic	47 (55.29%)	30 (56.60%)		
Nodular	11 (12.94%)	8 (15.09%)		
Ulcerative	15 (17.65%)	9 (16.98%)		
Erosive	12 (14.12%)	6 (11.32%)		
Depth of muscle infiltration, n (%)			0.041	0.839
≥1/2	45 (52.94%)	29 (54.72%)		
<1/2	40 (47.06%)	24 (45.28%)		
Vascular cancer thrombus status, n (%)			0.146	0.702
Yes	20 (23.53%)	14 (26.42%)		
No	65 (76.47%)	39 (73.58%)		

Table 1. Continued.

Variables	Training set (n = 85)	Test set (n = 53)	t/χ^2	p
Tumor markers in serum				
SCC-Ag (ng/mL)	3.11 ± 0.98	3.15 ± 0.93	0.167	0.868
CYFRA 21-1 (ng/mL)	3.60 ± 1.09	3.65 ± 1.12	0.217	0.829
CA125 (U/mL)	26.78 ± 6.83	26.20 ± 6.97	0.475	0.636
CEA (ng/mL)	2.01 ± 0.65	2.05 ± 0.62	0.316	0.752

BMI, body mass index; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CYFRA 21-1, cytokeratin fragment 21-1; FIGO, international federation of gynecology and obstetrics; LNM, lymph node metastasis; SCC-Ag, squamous cell carcinoma antigen.
FIGO staging definitions (based on FIGO 2018 criteria [6]): IA, microinvasive carcinoma with stromal invasion ≤5 mm in depth; IB, clinically visible lesion confined to the cervix or lesion >IA but ≤4 cm in size; IIA, tumor invades beyond the cervix to the upper two-thirds of the vagina but not to the parametrium.

Table 2. Comparison of demographic characteristics between the without LNM and with LNM groups in the training set.

Variables	Without LNM group (n = 63)	With LNM group (n = 22)	t/χ^2	p
Age (years)	60.12 ± 6.37	61.48 ± 8.36	0.792	0.431
BMI (kg/m^2)	22.52 ± 1.64	22.45 ± 1.83	0.165	0.870
Ethnicity, n (%)			0.003	0.959
Han	58 (92.06%)	21 (95.45%)		
Others	5 (7.94%)	1 (4.55%)		
Menopause, n (%)			0.173	0.677
Yes	34 (53.97%)	13 (59.09%)		
No	29 (46.03%)	9 (40.91%)		
Smoking, n (%)			0.066	0.798
Yes	9 (14.29%)	2 (9.09%)		
No	54 (85.71%)	20 (90.91%)		
Hypertension, n (%)			0.062	0.803
Yes	16 (25.4%)	5 (22.73%)		
No	47 (74.6%)	17 (77.27%)		
Diabetes, n (%)			0.083	0.774
Yes	18 (28.57%)	7 (31.82%)		
No	45 (71.43%)	15 (68.18%)		
Family history of cervical cancer, n (%)			0.186	0.667
Yes	10 (15.87%)	2 (9.09%)		
No	53 (84.13%)	20 (90.91%)		

2.4 Statistical Analysis

This study utilized SPSS software (version 29.0; developed by SPSS Inc., Chicago, IL, USA) for statistical analysis, with a two-sided p-value < 0.05 indicating statistical significance. In this paper, continuous variables are reported as mean ± standard deviation (SD). The Shapiro–Wilk test was used to assess the normality of continuous variables. For data that followed a normal distribution, independent t-tests were used for between-group comparisons. For data that did not conform to the normal distribution, the Mann–Whitney U test was used for between-group comparisons. The Chi-square tests were employed to compare categorical variables, which are expressed as frequencies and percentages in this paper. Dataset comparisons were initially performed to ensure uniform data distribution of all variables across the two datasets, followed by group comparisons. The dependent variable was the presence or absence of LNM in cervical cancer patients (yes = 1, no = 0). Independent variables included indicators with significant group differences ($p < 0.05$), which were analyzed through univariate and multivariate logistic regression analyses. Initially, univariate analysis was used to evaluate all potential independent variables to identify significant factors for inclusion in the multivariate logistic regression model. Before incorporating variables that were significant in the univariate analysis into the multivariate logistic regression model, we first performed multicollinearity diagnostics on these variables. In this study, we used variance inflation factor (VIF) and tolerance as diagnostic indicators, with VIF >10 or tolerance <0.1 indicating the presence of severe multicollinearity. The performance of the model was evaluated using calibration curve analysis,

Table 3. Comparison of disease features between the without LNM and with LNM groups in the training set.

Variables	Without LNM group (n = 63)	With LNM group (n = 22)	t/χ^2	p
Pathological type, n (%)			0.291	0.864
Squamous cell carcinoma	55 (87.30%)	20 (90.91%)		
Adenocarcinoma	5 (7.94%)	1 (4.55%)		
Adenosquamous carcinoma	3 (4.76%)	1 (4.55%)		
FIGO staging, n (%)			11.517	0.003
IA	27 (42.86%)	6 (27.27%)		
IB	25 (39.68%)	4 (18.18%)		
IIA	11 (17.46%)	12 (54.55%)		
Tumor diameter (cm)	2.35 $\pm$ 0.68	3.22 $\pm$ 0.95	4.638	0.001
Degree of differentiation, n (%)			10.876	0.004
Poorly differentiated	23 (36.51%)	17 (77.27%)		
Moderately differentiated	32 (50.79%)	4 (18.18%)		
Highly differentiated	8 (12.70%)	1 (4.55%)		
Appearance type, n (%)			1.509	0.680
Exophytic	34 (53.97%)	13 (59.09%)		
Nodular	7 (11.11%)	4 (18.18%)		
Ulcerative	12 (19.05%)	3 (13.64%)		
Erosive	10 (15.87%)	2 (9.09%)		
Depth of myometrial invasion, n (%)			7.054	0.008
$\geq$1/2	28 (44.44%)	17 (77.27%)		
$<$1/2	35 (55.56%)	5 (22.73%)		
Vascular cancer thrombus status, n (%)			7.930	0.005
Yes	10 (15.87%)	10 (45.45%)		
No	53 (84.13%)	12 (54.55%)		

receiver operating characteristic (ROC) curve analysis, and decision curve analysis (DCA).

3. Results

3.1 Comparison Between Datasets

The comparison of all data between the training set (n = 85) and the test set (n = 53) revealed no significant differences across all parameters examined (all $p > 0.05$) (Table 1, Ref. [6]). The overall trends suggest a high level of similarity between the training and test sets for all evaluated parameters, indicating that the distribution of patient characteristics and disease features is consistent across both datasets. This consistency supports the reliability of these datasets for model development and validation. The lack of significant differences also implies that any observed effects in subsequent analyses are more likely attributable to the variables under investigation rather than baseline differences in sample composition.

3.2 Training Set

3.2.1 Demographic Characteristics in the Training Set

The comparison of demographic characteristics between the without LNM group (n = 63) and the with LNM group (n = 22) in the training set revealed no significant differences across most parameters (Table 2). There were no significant differences in age (p = 0.431), BMI (p = 0.870), ethnicity (p = 0.959), menopause status (p = 0.677), smoking history (p = 0.798), hypertension (p = 0.803), diabetes (p = 0.774), or family history of cervical cancer (p = 0.667).

3.2.2 Disease Features in the Training Set

There were no significant differences in pathological type (p = 0.864) or appearance type (p = 0.680) between the without LNM and the with LNM groups in the training set (Table 3). However, notable differences were observed in FIGO staging (χ^2 = 11.517, p = 0.003), tumor diameter (t = 4.638, p = 0.001), degree of differentiation (χ^2 = 10.876, p = 0.004), depth of muscle infiltration (χ^2 = 7.054, p = 0.008), and vascular cancer thrombus status (χ^2 = 7.930, p = 0.005).

3.2.3 Measurements of Tumor Markers in the Training Set

Serum SCC-Ag levels were significantly higher in the with LNM group (3.87 $\pm$ 1.23 ng/mL) compared to the without LNM group (2.82 $\pm$ 0.65 ng/mL) (t = 5.074, $p <$ 0.001) (Table 4). Similarly, CYFRA 21-1 levels were significantly elevated in the with LNM group (4.32 $\pm$ 1.16 ng/mL vs 3.35 $\pm$ 0.98 ng/mL) (t = 3.815, $p <$ 0.001). CA125 levels were also significantly higher in the with LNM group (30.89 $\pm$ 8.45 U/mL vs 25.34 $\pm$ 5.72 U/mL) (t = 3.437, $p <$ 0.001). In contrast, CEA levels did not differ significantly between the two groups (without LNM: 1.95 $\pm$ 0.54 ng/mL vs with LNM: 2.18 $\pm$ 0.72 ng/mL, p = 0.120).

Table 4. Comparison of tumor markers between the without LNM and with LNM groups in the training set.

Tumor markers	Without LNM group (n = 63)	With LNM group (n = 22)	t	p
SCC-Ag (ng/mL)	2.82 ± 0.65	3.87 ± 1.23	5.074	<0.001
CYFRA 21-1 (ng/mL)	3.35 ± 0.98	4.32 ± 1.16	3.815	<0.001
CA125 (U/mL)	25.34 ± 5.72	30.89 ± 8.45	3.437	<0.001
CEA (ng/mL)	1.95 ± 0.54	2.18 ± 0.72	1.572	0.120

Table 5. Univariate logistic regression analysis of risk factors for long-term LNM after cervical cancer surgery.

Parameters	Coefficient	SE	Wald	p	OR	95% CI
FIGO staging IB (vs IA)	0.847	0.401	4.463	0.035	2.333	1.064–5.115
FIGO staging IIA (vs IA)	1.552	0.493	9.871	0.002	4.722	1.893–11.782
Tumor diameter	1.349	0.338	15.892	<0.001	3.855	1.930–7.701
Degree of differentiation (highly differentiated)	−1.396	0.423	10.876	0.001	0.248	0.105–0.585
Depth of muscle infiltration ≥1/2	1.446	0.545	7.054	0.008	4.250	1.477–12.230
Vascular cancer thrombus status	1.485	0.546	7.410	0.006	4.417	1.510–12.920
SCC-Ag	0.767	0.218	12.341	<0.001	2.153	1.458–3.181
CYFRA 21-1	1.032	0.269	15.627	<0.001	2.805	1.657–4.750
CA125	0.122	0.040	8.912	0.003	1.130	1.048–1.231

CI, confidence interval; OR, odds ratio; SE, standard error.

3.2.4 Univariate Logistic Regression Analysis

The univariate logistic regression analysis of risk factors for long-term LNM after cervical cancer surgery in the training set identified several significant factors (Table 5). Compared to stage IA, the risk was significantly higher in stage IIA patients (odds ratio [OR] = 4.722, 95% confidence interval [CI]: 1.893–11.782, p = 0.002) and in stage IB patients (OR = 2.333, 95% CI: 1.064–5.115, p = 0.035). Tumor diameter also emerged as a critical factor, showing a strong association with increased risk (OR = 3.855, 95% CI: 1.930–7.701, $p < 0.001$). Conversely, degree of differentiation (highly differentiated) was inversely related to LNM risk (OR = 0.248, 95% CI: 0.105–0.585, p = 0.001). Additionally, muscle infiltration depth ≥1/2 (OR = 4.250, 95% CI: 1.477–12.230, p = 0.008), presence of vascular cancer thrombus (OR = 4.417, 95% CI: 1.510–12.920, p = 0.006), elevated levels of SCC-Ag (OR = 2.153, 95% CI: 1.458–3.181, $p < 0.001$), CYFRA 21-1 (OR = 2.805, 95% CI: 1.657–4.750, $p < 0.001$), and CA125 (OR = 1.130, 95% CI: 1.048–1.231, p = 0.003) were all found to be significant predictors of LNM. Multicollinearity diagnostics were performed on the significant variables identified in the univariate analysis. The results showed that all variables had a VIF which was far below the threshold of 10 (maximum VIF = 2.1) and a tolerance well above 0.1 (minimum tolerance = 0.48). This indicated that there were no serious multicollinearity issues, so all these candidate variables were retained for the subsequent multivariate logistic regression analysis.

3.2.5 Multivariate Logistic Regression Analysis

The multivariate logistic regression analysis of risk factors for long-term LNM after cervical cancer surgery in the training set identified several significant factors (Table 6). Serum SCC-Ag (OR = 2.153, 95% CI: 1.199–3.867, p = 0.010) and CYFRA 21-1 (OR = 2.805, 95% CI: 1.611–4.887, $p < 0.001$) were significantly associated with an increased risk of long-term LNM. Statistically, CA125 was only marginally significant with a p-value slightly exceeding 0.05 (OR = 1.078, 95% CI: 0.997–1.166, p = 0.060). In contrast, FIGO staging IB (vs IA) (p = 0.399), FIGO staging IIA (vs IA) (p = 0.187), tumor diameter (p = 0.264), degree of differentiation (p = 0.382), depth of muscle infiltration (p = 0.198), and vascular cancer thrombus status (p = 0.412) did not show significant associations with long-term LNM.

3.2.6 ROC Analysis

The ROC analysis assessed the diagnostic value of two factors for long-term LNM following cervical cancer surgery in the training set (Table 7). Serum SCC-Ag achieved a sensitivity of 0.636 and specificity of 0.921, with an area under the curve (AUC) of 0.794. CYFRA 21-1 achieved a sensitivity of 0.636 and specificity of 0.889, with an AUC of 0.756. The AUC of the combined model in the training set was 0.869, demonstrating good discriminative ability. Furthermore, the combined model exhibited good performance on the test set that was highly consistent with the training set (AUC: 0.861). The sensitivity, specificity, Youden's index, and F1 score of the combined model were similar between the training and test sets, demonstrating the model's good generalization ability.

3.2.7 Establishment and Evaluation of the Diagnostic Model

Based on the multivariate analysis, serum SCC-Ag and CYFRA 21-1 were identified as significant predictors and used to construct a nomogram diagnostic model for

Table 6. Multivariate logistic regression analysis of risk factors for long-term LNM after cervical cancer surgery.

Variables	Coefficient	SE	Wald	*p*	OR	95% CI
FIGO staging IB (vs IA)	0.412	0.489	0.710	0.399	1.510	0.579–3.937
FIGO staging IIA (vs IA)	0.842	0.621	1.837	0.187	2.321	0.687–7.842
Tumor diameter	0.315	0.278	1.284	0.264	1.370	0.794–2.364
Degree of differentiation (highly differentiated)	–0.427	0.485	0.775	0.382	0.653	0.252–1.691
Depth of muscle infiltration $\geq$1/2	0.586	0.452	1.681	0.198	1.797	0.741–4.358
Vascular cancer thrombus status	0.329	0.398	0.683	0.412	1.390	0.637–3.032
SCC-Ag	0.767	0.299	6.583	0.010	2.153	1.199–3.867
CYFRA 21-1	1.032	0.283	13.303	<0.001	2.805	1.611–4.887
CA125	0.075	0.040	3.516	0.060	1.078	0.997–1.166

Table 7. ROC analysis of factors for predicting long-term LNM after cervical cancer surgery.

Variables	Best threshold	Sensitivity	Specificity	AUC (95% CI)	*p*	Youden's index	F1-score
SCC-Ag (ng/mL)	3.720	0.636	0.921	0.794 (0.680–0.908)	<0.001	0.557	0.683
CYFRA 21-1 (ng/mL)	4.410	0.636	0.889	0.756 (0.632–0.879)	0.001	0.525	0.651
Combined model in the training set	-	0.773	0.841	0.869 (0.782–0.955)	<0.001	0.614	0.758
Combined model in the test set	-	0.800	0.816	0.861 (0.751–0.971)	<0.001	0.616	0.762

AUC, area under the curve; ROC, receiver operating characteristic.

long-term LNM after cervical cancer surgery (Fig. 2A). The nomogram integrates these two markers to provide a comprehensive risk assessment tool. The calibration curve demonstrates good agreement between predicted and observed outcomes, validating the model's accuracy (Fig. 2B). The ROC curve shows an AUC of 0.869, indicating high discriminatory power for predicting long-term LNM (Fig. 2C). Additionally, the decision curve analysis confirms the clinical utility of this model by illustrating its net benefit across different threshold probabilities (Fig. 2D).

3.3 Test Set

3.3.1 Measurements of Tumor Markers in the Test Set

Serum SCC-Ag levels were significantly higher in the with LNM group (3.91 $\pm$ 1.25 ng/mL) compared to the without LNM group (2.85 $\pm$ 0.68 ng/mL) (t = 3.976, $p <$ 0.001; Table 8). Similarly, CYFRA 21-1 levels were significantly elevated in the with LNM group (4.35 $\pm$ 1.15 ng/mL vs 3.38 $\pm$ 1.01 ng/mL) (t = 3.014, p = 0.004). CA125 levels were also significantly higher in the with LNM group (30.95 $\pm$ 9.58 U/mL vs 24.33 $\pm$ 3.75 U/mL) (t = 3.649, $p <$ 0.001). There was no significant difference in CEA levels between the two groups (without LNM: 1.98 $\pm$ 0.46 ng/mL vs with LNM: 2.21 $\pm$ 0.65 ng/mL) (t = 1.453, p = 0.152).

3.3.2 ROC Prediction Model in the Test Set

The ROC curve in the test set for predicting long-term LNM after cervical cancer surgery using SCC-Ag combined with CYFRA 21-1 showed an AUC of 0.861, consistent with findings from the training set, confirming the robustness and reliability of this diagnostic model (Fig. 3A). The calibration curve showed good agreement between predicted probabilities and observed frequencies (Fig. 3B). The DCA curve indicated that using this combined model for clinical decision-making yields a net benefit across a wide range of probability thresholds (Fig. 3C).

4. Discussion

The present study aimed to evaluate the diagnostic value of serum SCC-Ag combined with CYFRA 21-1 for long-term LNM after cervical cancer surgery. Our findings indicate that these tumor markers may serve as valuable indicators in predicting the risk of LNM, particularly when used in combination. While demographic characteristics and certain disease features did not differ significantly between patients with and without LNM, notable differences were observed in FIGO staging, tumor diameter, degree of differentiation, depth of muscle infiltration, and the presence of vascular cancer thrombus. In terms of tumor markers, our results demonstrate that serum levels of SCC-Ag and CYFRA 21-1 were elevated in patients with LNM compared to those without. SCC-Ag is known to be overexpressed in squamous cell carcinomas, including cervical cancer, and its elevation has been linked to more aggressive disease phenotypes [21,22]. The mechanism behind this association likely involves the role of SCC-Ag in promoting tumor proliferation and invasion through various pathways, such as the activation of matrix metalloproteinases (MMPs) [23,24]. MMPs degrade extracellular matrix components, facilitating tumor cell migration and metastasis [25,26]. Similarly, CYFRA 21-1, a fragment of cytokeratin 19, is elevated in several malignancies, including cervical cancer. Its increased levels may reflect the breakdown of epithelial structures during tumor progression, indicating

Table 8. Comparison of tumor markers between the without LNM and with LNM groups in the test set.

Tumor markers	Without LNM group (n = 38)	With LNM group (n = 15)	t	p
SCC-Ag (ng/mL)	2.85 ± 0.68	3.91 ± 1.25	3.976	<0.001
CYFRA 21-1 (ng/mL)	3.38 ± 1.01	4.35 ± 1.15	3.014	0.004
CA125 (U/mL)	24.33 ± 3.75	30.95 ± 9.58	3.649	<0.001
CEA (ng/mL)	1.98 ± 0.46	2.21 ± 0.65	1.453	0.152

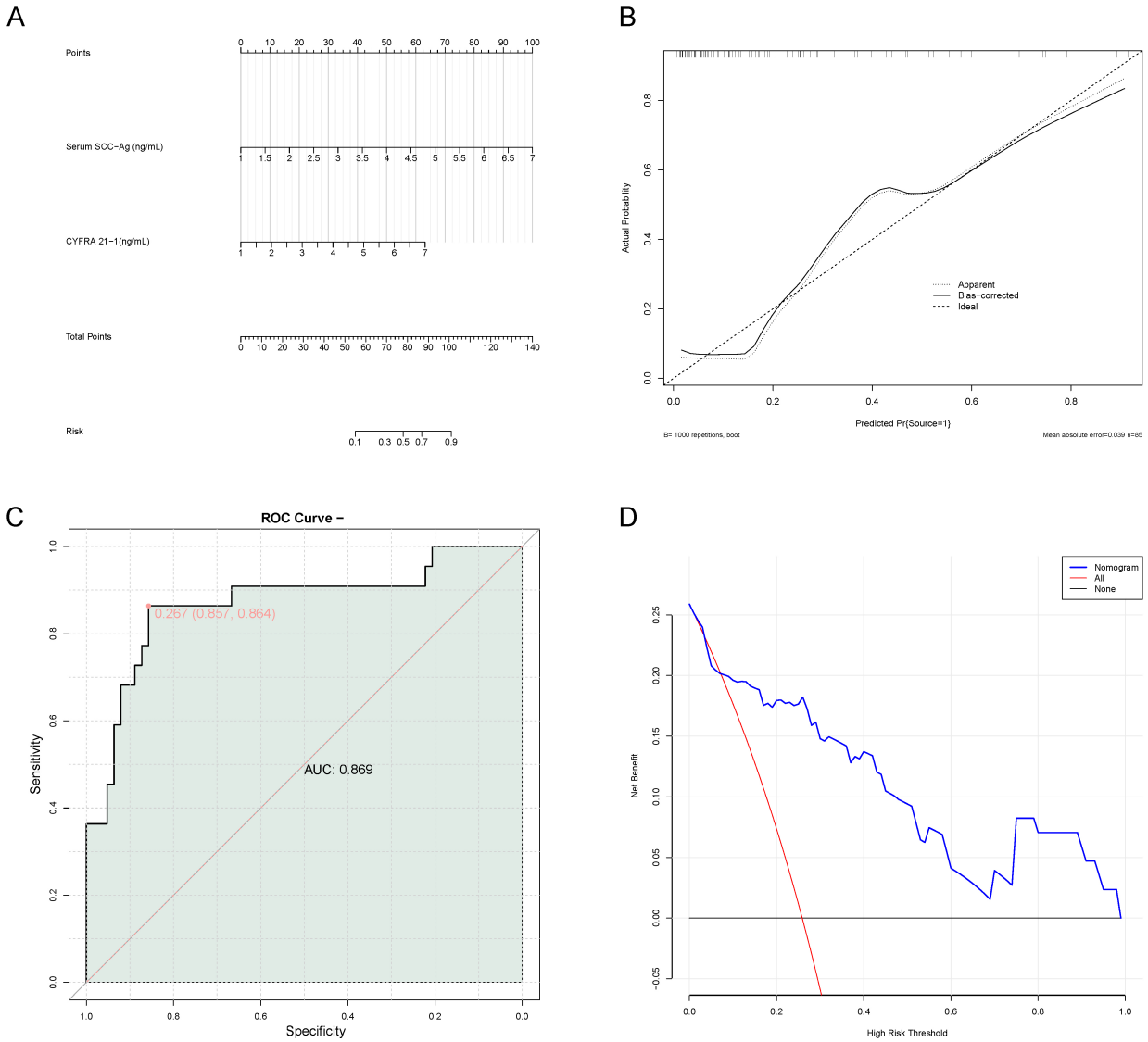

Fig. 2. A nomogram-based diagnostic model integrating SCC-Ag and CYFRA 21-1 for predicting long-term LNM after cervical cancer surgery. (A) Nomogram. (B) Calibration curve. (C) ROC curve. (D) DCA. DCA, decision curve analysis.

an active process of cellular turnover and metastatic spread [27].

The multivariate logistic regression analysis identified serum SCC-Ag and CYFRA 21-1 as independent predictors of long-term LNM, suggesting their potential utility in clinical practice. This finding aligns with existing literature, where SCC-Ag and CYFRA 21-1 have been shown to correlate with adverse outcomes in cervical cancer [23,28,29]. For instance, a study by Gu *et al.* [30] found that elevated levels of SCC-Ag were associated with poorer prognosis in cervical cancer patients. However, unlike our study, Gu *et al.* [30] did not investigate the combined diagnostic value of SCC-Ag and CYFRA 21-1, highlighting the novelty of our approach.

The ROC analysis further supports the diagnostic power of these markers, particularly when used together. Serum SCC-Ag showed high specificity but moderate sensitivity, while CYFRA 21-1 demonstrated the same sensitivity but with a relatively lower specificity. Combining these markers into a nomogram model improved the over-

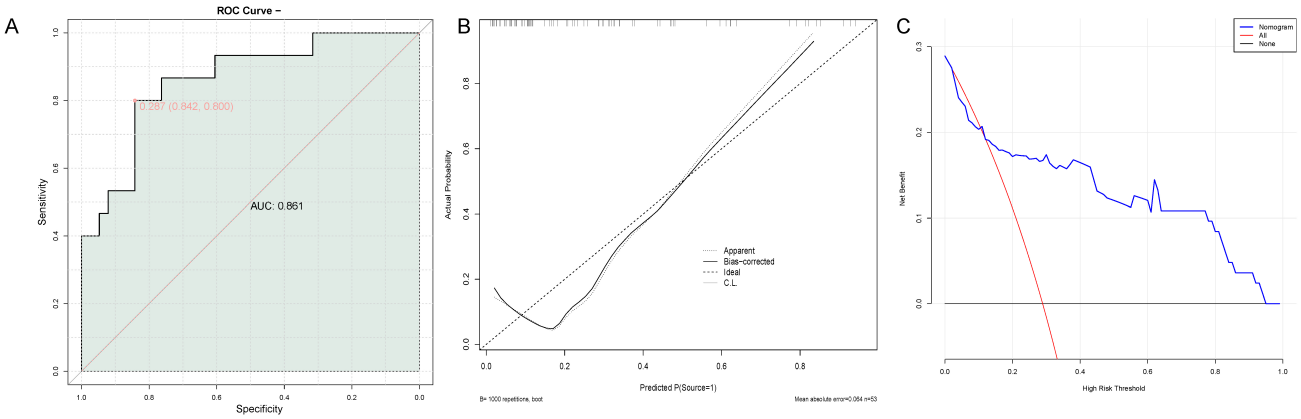

Fig. 3. ROC curve analysis of SCC-Ag combined with CYFRA 21-1 in the test set for predicting long-term LNM after cervical cancer surgery. (A) ROC curve. (B) Calibration curve. (C) DCA.

all discriminatory ability, as evidenced by the higher AUC. This suggests that the integration of multiple biomarkers can enhance diagnostic accuracy, providing a more comprehensive assessment of individual patient risk. Such models could potentially guide personalized treatment strategies, optimizing therapeutic interventions based on predicted metastatic risk.

The mechanisms underlying the association of elevated SCC-Ag and CYFRA 21-1 levels with LNM are complex and multifactorial. One possible explanation is the involvement of these markers in epithelial-mesenchymal transition (EMT), a critical process in cancer metastasis [31,32]. EMT enables epithelial cells to acquire mesenchymal properties, enhancing their migratory and invasive capabilities [33–35]. SCC-Ag and CYFRA 21-1 may play roles in modulating this transition, either directly or indirectly through interactions with signaling cascades such as transforming growth factor-β (TGF-β) and Wnt/β-catenin pathways [36,37].

One limitation of our study is its retrospective design, which inherently introduces biases and limits the generalizability of our findings. Retrospective studies rely on existing data that may not have been collected with the specific research question in mind, potentially leading to incomplete or inconsistent datasets. For instance, variations in patient follow-up schedules, differences in imaging protocols, and inconsistencies in pathological assessments could all contribute to variability in the study outcomes. Selection bias may occur if certain patients were more likely to be included in the study based on their clinical characteristics or availability of complete medical records. These factors can affect the reliability of the diagnostic model and necessitate cautious interpretation of the results. Despite rigorous inclusion and exclusion criteria, the retrospective nature of the study means that unmeasured confounders might still influence the observed associations between biomarkers and LNM. Therefore, while our findings are promising, they require further validation through prospective studies with larger sample sizes and more standardized data collection methods. Secondly, our study identified an age distribution in our sample that was older than what is typically seen at the onset of cervical cancer. This discrepancy could be influenced by regional healthcare practices, delayed diagnosis, and differences in screening accessibility. Future studies should aim to include a broader and more representative sample of patients to better align with the general epidemiology of cervical cancer. Additionally, investigating the reasons behind this older age distribution could provide valuable insights into regional patterns and help tailor preventive strategies accordingly. Thirdly, the relatively small sample size (n = 138) and the limited number of outcome events (n = 22) in this study warrant caution in interpreting the multivariate logistic regression results. With 8 candidate variables entered into the final model, the events-per-variable (EPV) ratio was approximately 2.44, which is well below the generally recommended threshold of 10. A low EPV can lead to model overfitting, unstable coefficient estimates, and overly optimistic performance measures that may not generalize to external populations. Therefore, the diagnostic model developed in this study should be considered exploratory, and external validation in larger independent cohorts is necessary before clinical application.

Prospective studies with larger sample sizes would provide more robust evidence and validate the diagnostic model developed in this study. Such studies should aim to include diverse populations across different geographic regions and healthcare systems to ensure broad applicability and generalizability. Future investigations should explore other potential biomarkers beyond serum markers to enhance the diagnostic accuracy of LNM. Genetic mutations, microRNA expression profiles, and immune-related biomarkers represent promising avenues for further research. For example, certain genetic mutations and epigenetic modifications have been shown to correlate with increased metastatic potential and poor prognosis in various cancers. Similarly, microRNAs, small non-coding RNAs

that regulate gene expression, have emerged as key regulators of tumor progression and metastasis. Investigating these additional biomarkers could provide a more comprehensive understanding of the molecular mechanisms underlying cervical cancer metastasis and facilitate their adoption for improving risk stratification. The clinical utility of the nomogram model requires validation in diverse populations and settings to ensure its applicability across different healthcare systems. This includes assessing its performance in real-world clinical practice and evaluating its impact on patient management decisions. By integrating multiple types of biomarkers and validating the model in broader contexts, future research can pave the way for more personalized and effective treatment strategies for cervical cancer patients, ultimately improving outcomes and quality of life.

Taken together, our study highlights the potential of serum SCC-Ag and CYFRA 21-1 as diagnostic markers for long-term LNM after cervical cancer surgery. The combination of these markers into a nomogram model offers enhanced diagnostic accuracy, guiding personalized treatment decisions. Understanding the underlying mechanisms linking these markers to metastatic processes will be crucial for developing targeted therapies and improving survival rates in cervical cancer patients.

5. Conclusion

This study suggests that the combination of serum SCC-Ag and CYFRA 21-1 may hold potential as a valuable tool for predicting long-term LNM after cervical cancer surgery. Both markers were found to be elevated in patients who developed LNM compared to those who did not, indicating their possible role in identifying high-risk patients. The constructed nomogram model integrating SCC-Ag and CYFRA 21-1 demonstrated promising discriminatory power, potentially enhancing the accuracy of LNM prediction. While these findings are encouraging, further large-scale prospective studies are necessary to validate these preliminary observations and to establish standardized protocols for clinical application. Future research should also explore the underlying mechanisms linking these biomarkers to metastatic processes and investigate additional biomarkers to refine risk assessment models.

Key Points

• This study demonstrates that preoperative serum levels of SCC-Ag and CYFRA 21-1 are significantly elevated in cervical cancer patients who develop long-term LNM following radical surgery, identifying both markers as independent predictors for this adverse outcome.

• A nomogram-based diagnostic model integrating SCC-Ag and CYFRA 21-1 was developed and validated, showing high discriminatory power with AUC values of 0.869 in the training set and 0.861 in the test set, providing a practical tool for individualized risk assessment.

• The combination of SCC-Ag and CYFRA 21-1 outperformed either marker alone in predicting long-term LNM, suggesting that their combined use offers enhanced diagnostic accuracy compared to relying on a single biomarker.

• The diagnostic model demonstrated good calibration and clinical utility across a range of threshold probabilities in the decision curve analysis, supporting its potential for guiding personalized adjuvant treatment by identifying high-risk patients who might benefit from more intensive surveillance or therapy.

• These findings underscore the significant clinical value of integrating these serum biomarkers into the postoperative management and risk stratification of patients with early-stage cervical cancer, potentially improving outcomes through earlier intervention.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

KZX conceived the study; designed the methodology; collected and analyzed the data; drafted the initial manuscript. GLZ supervised the research; validated the data analysis. Both authors have been involved in revising it critically for important intellectual content. Both authors approved the final version. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This research constitutes a retrospective analysis adhering to medical ethics guidelines and the principles of the Declaration of Helsinki. The study protocol received approval from the Institutional Review Board (IRB) of Shandong Public Health Clinical Center, which granted a waiver of obtaining informed consent since the study relied on previously collected anonymized clinical data and did not involve any additional interventions for patients, and all personally identifiable information, including names, hospital numbers, and ID numbers, were excluded during data processing to safeguard patient privacy (Approval Number: GWLCZXEC-SOP-K-2025-203).

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Singh D, Vignat J, Lorenzoni V, Eslahi M, Ginsburg O, Lauby-Secretan B, *et al*. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. The Lancet. Global Health. 2023; 11: e197–e206. https://doi.org/10.1016/S2214-109X(22)00501-0.

[2] Pimple SA, Mishra GA. Global strategies for cervical cancer prevention and screening. Minerva Ginecologica. 2019; 71: 313–320. https://doi.org/10.23736/S0026-4784.19.04397-1.

[3] Rahangdale L, Mungo C, O'Connor S, Chibwesha CJ, Brewer NT. Human papillomavirus vaccination and cervical cancer risk. BMJ (Clinical Research Ed.). 2022; 379: e070115. https://doi.org/10.1136/bmj-2022-070115.

[4] Xu M, Cao C, Wu P, Huang X, Ma D. Advances in cervical cancer: current insights and future directions. Cancer Communications. 2025; 45: 77–109. https://doi.org/10.1002/cac2.12629.

[5] Re GL, Cucinella G, Zaccaria G, Crapanzano A, Salerno S, Pinto A, *et al*. Role of MRI in the Assessment of Cervical Cancer. Seminars in Ultrasound, CT, and MR. 2023; 44: 228–237. https://doi.org/10.1053/j.sult.2023.03.010.

[6] Saleh M, Virarkar M, Javadi S, Elsherif SB, de Castro Faria S, Bhosale P. Cervical Cancer: 2018 Revised International Federation of Gynecology and Obstetrics Staging System and the Role of Imaging. AJR. American Journal of Roentgenology. 2020; 214: 1182–1195. https://doi.org/10.2214/AJR.19.21819.

[7] Zhu Y, Fu C, Du J, Jin Y, Du S, Zhao F. Prediction of Cervical Cancer Lymph Node Metastasis via a Multimodal Transfer Learning Approach. British Journal of Hospital Medicine. 2024; 85: 1–14. https://doi.org/10.12968/hmed.2024.0428.

[8] Yuan L, Jiang H, Jia Y, Liao Y, Shao C, Zhou Y, *et al*. Fatty Acid Oxidation Supports Lymph Node Metastasis of Cervical Cancer via Acetyl-CoA-Mediated Stemness. Advanced Science. 2024; 11: e2308422. https://doi.org/10.1002/advs.202308422.

[9] Mei X, Xiong J, Liu J, Huang A, Zhu D, Huang Y, *et al*. DHCR7 promotes lymph node metastasis in cervical cancer through cholesterol reprogramming-mediated activation of the KANK4/PI3K/AKT axis and VEGF-C secretion. Cancer Letters. 2024; 584: 216609. https://doi.org/10.1016/j.canlet.2024.216609.

[10] He H, He M, Zhou Q, Tang Y, Wang J, Li X, *et al*. Genetic analysis of cervical cancer with lymph node metastasis. Journal of Gynecologic Oncology. 2024; 35: e102. https://doi.org/10.3802/jgo.2024.35.e102.

[11] Jin L, Cao F, Zhang Y, Dang Y, Wang F. Nomograms for predicting prognostic value of combined neutrophil-to-lymphocyte ratio and SCC-Ag in locally advanced cervical cancer. Translational Cancer Research. 2024; 13: 1323–1335. https://doi.org/10.21037/tcr-23-1501.

[12] Jiang CZ, Zheng K, Zhang YY, Yang J, Ye H, Peng X. ^{18}F-FDG PET/CT semi-quantitative parameters combined with SCC-Ag in predicting lymph node metastasis in stage I-II cervical cancer. Frontiers in Oncology. 2024; 14: 1278464. https://doi.org/10.3389/fonc.2024.1278464.

[13] Zhang M, Xin L, Cheng B, Yan B, Zhen J, Yang C, *et al*. Clinical Value Analysis of Serum TK1, SCC-Ag, and MUC-1 in the Diagnosis and Prognosis Evaluation of Cervical Cancer. Alternative Therapies in Health and Medicine. 2023; 29: 788–792.

[14] Park J, An S, Kim K, Kim JS, Jung CK, Bae JS. Diagnostic utilities of washout CYFRA 21-1 combined with washout thyroglobulin for metastatic lymph nodes in thyroid cancer: a prospective study. Scientific Reports. 2024; 14: 7599. https://doi.org/10.1038/s41598-024-58093-9.

[15] Chen F, Zhang X. Predictive value of serum SCCA and CYFRA21-1 levels on radiotherapy efficacy and prognosis in patients with non-small cell lung cancer. Biotechnology & Genetic Engineering Reviews. 2024; 40: 4205–4214. https://doi.org/10.1080/02648725.2023.2208449.

[16] Ishioka N, Suzuki T, Yajima S, Murakami K, Ohkura Y, Fukuda T, *et al*. Prognostic Impact of Pretreatment Serum CYFRA Status in 1047 Patients with Esophageal Squamous Cell Carcinoma Who Underwent Radical Resection: A Japan Esophageal Society Promotion Research. Annals of Thoracic and Cardiovascular Surgery. 2022; 28: 163–170. https://doi.org/10.5761/atcs.oa.21-00195.

[17] Zeng S, Li X, Xiao S, Yang P, Lin C, Chen H, *et al*. Prognostic evaluation and treatment strategies for cervical cancer in pregnancy: a systematic review and meta-analysis. BMC Cancer. 2025; 25: 502. https://doi.org/10.1186/s12885-025-13827-4.

[18] Rao Q, Han X, Wei Y, Zhou H, Gong Y, Guan M, *et al*. Novel prognostic nomograms in cervical cancer based on analysis of 1075 patients. Cancer Medicine. 2023; 12: 6092–6104. https://doi.org/10.1002/cam4.5335.

[19] Klotz DM, Link T, Wimberger P, Kuhlmann JD. A predictive and prognostic model for surgical outcome and prognosis in ovarian cancer computed by clinico-pathological and serological parameters (CA125, HE4, mesothelin). Clinical Chemistry and Laboratory Medicine. 2023; 62: 530–539. https://doi.org/10.1515/cclm-2023-0314.

[20] Abu-Rustum NR, Yashar CM, Bean S, Bradley K, Campos SM, Chon HS, *et al*. NCCN Guidelines Insights: Cervical Cancer, Version 1.2020. Journal of the National Comprehensive Cancer Network. 2020; 18: 660–666. https://doi.org/10.6004/jnccn.2020.0027.

[21] Zheng X, Shen F, Chen W, Ren W, Tang S. Integrated pretreatment diffusion kurtosis imaging and serum squamous cell carcinoma antigen levels: a biomarker strategy for early assessment of radiotherapy outcomes in cervical cancer. Abdominal Radiology. 2024; 49: 1502–1511. https://doi.org/10.1007/s00261-024-04270-3.

[22] Zhang XY, Xu C, Wu XC, Qu QQ, Deng K. Evaluation of Amide Proton Transfer Imaging Combined With Serum Squamous Cell Carcinoma Antigen for Grading Cervical Cancer. Journal of Computer Assisted Tomography. 2025; 49: 399–406. https://doi.org/10.1097/RCT.0000000000001699.

[23] Shi L, Liu Y, Li J, Kou J, Ouyang Y, Chen F, *et al*. Establishment of a risk stratification model based on the combination of post-treatment serum squamous cell carcinoma antigen levels and FIGO stage of cervical cancer for treatment and surveillance decision-making. Journal of Cancer Research and Clinical Oncology. 2023; 149: 5999–6007. https://doi.org/10.1007/s00432-022-04558-1.

[24] Qin L. Study on the preoperative value of serum SCC-Ag in predicting the stromal invasion of cervical squamous cell carcinoma. Journal of Cancer Research and Clinical Oncology. 2023; 149: 9167–9171. https://doi.org/10.1007/s00432-023-04836-6.

[25] Wang H, Li X, Zhou S, Guo W, Wang Z, Sun L, *et al*. Integrated analysis of single-cell RNA-seq and bulk RNA-seq reveals *MMP* mediated expression patterns by distinct tumor microenvironment immune profiles in cervical cancer. Journal of Cancer. 2024; 15: 5258–5276. https://doi.org/10.7150/jca.96429.

[26] Padežnik T, Oleksy A, Cokan A, Takač I, Sobočan M. Changes in the Extracellular Matrix in Endometrial and Cervical Cancer: A Systematic Review. International Journal of Molecular Sciences. 2023; 24: 5463. https://doi.org/10.3390/ijms24065463.

[27] Pedraza S, Seiffert AP, Sarandeses P, Muñoz-Lopez B, Gómez EJ, Sánchez-González P, *et al*. The value of metabolic parameters and textural analysis in predicting prognosis in lo-

cally advanced cervical cancer treated with chemoradiotherapy. Strahlentherapie und Onkologie. 2022; 198: 792–801. https://doi.org/10.1007/s00066-022-01900-x.

[28] Tony V, Sathyamurthy A, Ramireddy JK, Iswarya SJ, Gowri SM, Thomas A, *et al*. Role of squamous cell carcinoma antigen in prognostication, monitoring of treatment response, and surveillance of locally advanced cervical carcinoma. Journal of Cancer Research and Therapeutics. 2023; 19: 1236–1240. https://doi.org/10.4103/jcrt.jcrt_335_21.

[29] Shi V, Grover S, Huang Y, Thaker PH, Kuroki LM, Powell MA, *et al*. Accuracy of surveillance serum squamous cell carcinoma antigen for cervical cancer recurrence after definitive chemoradiation. International Journal of Gynecological Cancer. 2024; 34: 808–816. https://doi.org/10.1136/ijgc-2024-005303.

[30] Gu LN, Yu JW, Jiang L, Liu TB, Xu Y. Serum squamous cell carcinoma antigen level and magnetic resonance imaging for the prognosis of locally advanced cervical cancer. European Review for Medical and Pharmacological Sciences. 2024; 28: 668–678. https://doi.org/10.26355/eurrev_202401_35064.

[31] Xu F, Li Y, Fan L, Ma J, Yu L, Yi H, *et al*. Preoperative SCC-Ag and thrombocytosis as predictive markers for pelvic lymphatic metastasis of squamous cervical cancer in early FIGO stage. Journal of Cancer. 2018; 9: 1660–1666. https://doi.org/10.7150/jca.24049.

[32] Kawai T, Yasuchika K, Ishii T, Katayama H, Yoshitoshi EY, Ogiso S, *et al*. Identification of keratin 19-positive cancer stem cells associating human hepatocellular carcinoma using CYFRA 21-1. Cancer Medicine. 2017; 6: 2531–2540. https://doi.org/10.1002/cam4.1211.

[33] Zhao YC, Li YF, Qiu L, Jin SZ, Shen YN, Zhang CH, *et al*. SQLE-a promising prognostic biomarker in cervical cancer: implications for tumor malignant behavior, cholesterol synthesis, epithelial-mesenchymal transition, and immune infiltration. BMC Cancer. 2024; 24: 1133. https://doi.org/10.1186/s12885-024-12897-0.

[34] Yang X, Zhu W. ERBB3 mediates the PI3K/AKT/mTOR pathway to alter the epithelial-mesenchymal transition in cervical cancer and predict immunity filtration outcome. Experimental and Therapeutic Medicine. 2023; 25: 146. https://doi.org/10.3892/etm.2023.11845.

[35] Yang X, Sun F, Gao Y, Li M, Liu M, Wei Y, *et al*. Histone acetyltransferase CSRP2BP promotes the epithelial-mesenchymal transition and metastasis of cervical cancer cells by activating N-cadherin. Journal of Experimental & Clinical Cancer Research. 2023; 42: 268. https://doi.org/10.1186/s13046-023-02839-2.

[36] Liu P, Pei JJ, Li L, Li JW, Ke XP. Sildenafil Inhibits the Growth and Epithelial-to-mesenchymal Transition of Cervical Cancer via the TGF-β1/Smad2/3 Pathway. Current Cancer Drug Targets. 2023; 23: 145–158. https://doi.org/10.2174/1568009622666220816114543.

[37] Yang H, Ma X, Song B, Wang D, Chai Z. Golgi Phosphoprotein 3 Promotes Cervical Cancer Progression via Wnt/β-catenin Mediated Epithelial-Mesenchymal Transition. Annals of Clinical and Laboratory Science. 2023; 53: 738–748.