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Original Article

Establishment and validation of a recurrence risk model in early-stage tongue squamous cell carcinoma patients incorporating immune-inflammatory biomarkers and clinicopathological parameters

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Abstract: Objective: To develop and validate a machine learning-based predictive model incorporating immuno-inflammatory biomarkers and clinicopathological parameters to predict recurrence risk in early-stage tongue squamous cell carcinoma (TSCC) patients. Methods: This retrospective study included 515 early-stage TSCC patients treatment at Xinyu People's Hospital between May 2014 and May 2019. Medical records and laboratory data were reviewed. Patients were randomly divided into a training cohort (n=339) and a validation cohort (n=176). Feature selection was performed using LASSO, Xgboost, and Support Vector Machine (SVM) algorithms to identify key features associated with recurrence. A predictive nomogram was then built based on multivariate Cox regression analysis. Model performance was evaluated using receiver operating characteristic (ROC) curve analysis, calibration plots, and decision curve analysis (DCA). Results: Recurrence was observed in 160 cases (31.07%), with 111 (32.74%) in training cohort (n=339) and 49 (27.84%) in the validation cohort (n=176). Machine learning algorithms identified several key risk factors for recurrence, including immuno-inflammatory markers (e.g., white blood cell count [WBC], platelet count [PLT], C-reactive protein [CRP], neutrophil-to-lymphocyte ratio [NLR], systemic inflammation response index [SIRI], C-reactive protein-to-albumin ratio [CAR]) and clinicopathological characteristics (e.g., pathological classification, chemotherapy status, tumor location). The nomogram achieved areas under the ROC curve (AUCs) of 0.902 (95% CI: 0.866-0.937) in the training set and 0.819 (95% CI: 0.759-0.876) in the validation set. Calibration curves demonstrated good predictive consistency (P=0.621). DCA showed a clear net clinical benefit across a wide range of thresholds probabilities (P<0.001). Conclusion: This predictive model, integrating immuno-inflammatory markers and clinicopathological features, exhibits excellent predictive performance for recurrence risk in early-stage STCC and offers substantial clinical utility.

Keywords: Tongue Squamous Cell Carcinoma (TSCC), immuno-inflammatory markers, predictive model, machine learning, recurrence risk

Introduction

Growing evidence highlights the significant association between immune-inflammatory status and tumor recurrence. The tumor microenvironment, particularly immune cell infiltration and inflammatory activity, plays a critical role in carcinogenesis, progression, and relapse [1]. Kashima et al. [2] reported that increased accumulation of CD8+ T cells and regulatory T cells (Tregs) at the tumor periphery in oral tongue squamous cell carcinoma (TSCC) suggests a pivotal role for localized immune responses in facilitating tumor immune escape and recurrence. Supporting this, Cha et al. [3] utilized single-cell RNA sequencing to demonstrate the diverse responses to immunotherapy among HPV-positive oropharyngeal cancer

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patients. Their findings highlighted CD161+ resident memory T cells (Trm) as key contributors to suppressing tumor immune escape mechanisms, thus linking them to cancer recurrence. Furthermore, inflammatory mediators like tumor necrosis factor alpha (TNF-α) have been implicated in oral squamous cell carcinoma (OSCC)-associated pain and inflammation. Scheff et al. [4] demonstrated elevated TNF-α levels in both OSCC cell line supernatants and in 4NQO-induced murine tongue tissue, with its suppression effectively reducing cancer-related allodynia. Likewise, Thakore et al. [5] showed that the polyphenolic extract Polypodium leucotomos (PL) reprogrammed macrophage activation and attenuated tumor-promoting inflammatory responses, effectively restraining TSCC progression. These findings suggest that enhanced immune-inflammatory activity not only drives tumorigenesis but may also increase susceptibility to recurrence [6]. Consequently, the integration of immune-inflammatory biomarkers into existing prediction systems could offer a more comprehensive evaluation of patients' recurrence risk.

As the predominant variant of OSCC, TSCC presents unique challenges in head and neck oncology practice [7]. The tongue's unique anatomical features, including its vascularity, complex lymphatic drainage, and mobility, predispose patients to regional lymph node metastases and consequently, higher recurrence rates [8]. Current gold-standard treatment involving surgical excision with chemoradiotherapy still yields substantial recurrence rates, frequently accompanied by debilitating functional impairments due to the tongue's vital roles in speech, chewing, and swallowing [9]. The discrepancies between TNM staging and actual recurrence outcomes in clinically similar patients exposes the limitations of traditional staging systems, emphasizing the need for more sophisticated predictive models that integrate immune-inflammatory markers, histopathological features, and therapeutic variables. Such models would enable early intervention and improved prognosis. Advanced predictive methodologies, particularly nomograms and machine learning approaches, are increasingly demonstrating their utility in refining prognostic accuracy and advancing precision medicine.

In modern medical research, machine learning has become indispensable for diagnostic and prognostic applications, particularly in assessing disease risks [10]. By processing large-scale patient data, these computational techniques can identify critical disease-associated features and build reliable prognostic tools. These computational tools offer dual clinical benefits: improving diagnostic accuracy and enabling patient-specific risk forecasting, which supports early detection and customized therapeutic approaches [11]. Current approaches for predicting TSCC recurrence, while considering multiple clinical and pathological factors, often fall short due to insufficient incorporation of immune-inflammatory biomarkers. Many established prediction models depend on isolated clinical parameters or individual biomarkers, failing to capture the multidimensional nature of recurrence mechanisms. For example, Dikova et al. [12] found that multiplexed salivary cytokine analysis (IL-6, IL-8, and TNF-α) provided robust discrimination (area under the curve [AUC] >0.8) between OSCC and healthy controls. Similarly, Guo et al. [13] found that an integrated assessment of exosomal markers (CRP, VWF, and LRG) in serum provided better diagnostic value (high sensitivity and specificity) than any single marker for OSCC. This study's novel contribution involves incorporating a comprehensive panel of immune-inflammatory biomarkers into the predictive algorithm, facilitating a more robust and multidimensional assessment of recurrence risk.

The primary objective of this investigation is to develop and validate a recurrence prediction model utilizing immuno-inflammatory markers to assess recurrence probability in early-stage TSCC. Modern oncological studies have established inflammation as a significant contributor to tumor initiation and progression. Immuno-inflammatory markers, as key indicators of systemic inflammation and immune function, provide essential prognostic insight for cancer management. This research introduces an innovative approach by combining clinical data with immuno-inflammatory markers to construct an effective prediction model for early-stage TSCC patients.

Methods and materials

Sample source

This study was approved by the Ethics Committee of Xinyu People's Hospital and adhered

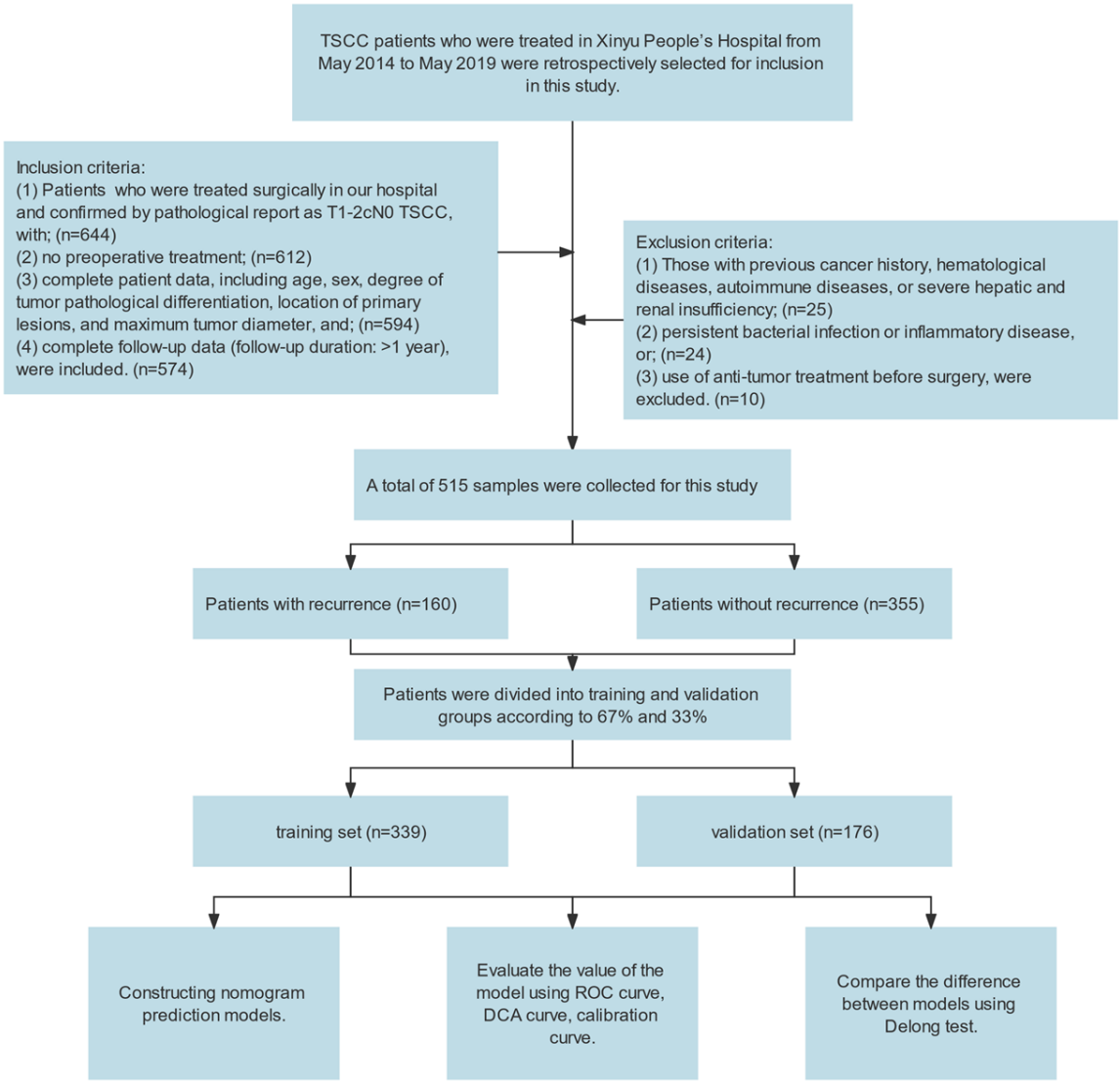

Figure 1. Study flow chart. Note: TSCC: Tongue Squamous Cell Carcinoma, ROC: Receiver Operating Characteristic, DCA: Decision Curve Analysis.

to the Declaration of Helsinki (**Figure 1**). TSCC patients treated at Xinyu People's Hospital between May 2014 and May 2019 were retrospectively enrolled.

Inclusion and exclusion criteria

Inclusion criteria: (1) pathologically confirmed T1-2cN0 TSCC; (2) no preoperative treatment; (3) complete patient data, including age, sex, degree of tumor pathological differentiation, location of primary lesions, and maximum tumor diameter; (4) complete follow-up data (follow-up duration: >1 year).

Exclusion criteria: (1) previous cancer history, hematological diseases, autoimmune diseases, or severe hepatic or renal insufficiency; (2) persistent bacterial infection or inflammatory disease; (3) use of anti-tumor treatment before surgery.

Sample screening and grouping

A total of 515 eligible cases (160 recurrent and 355 non-recurrent cases) were enrolled. These cases were then assigned to training (n=339) and validation sets (n=176) at a 66%:34% ratio.

Clinical data collection

The electronic medical record system and outpatient review records were retrieved for medical record and laboratory data collection. Clinical data mainly included age, sex, pathological classification, tumor location, tumor diameter, and use of radiotherapy/chemotherapy. Laboratory indicators included white blood cell count (WBC), platelet count (PLT), neutrophil count (NEUT), lymphocyte count (LYM), monocyte count (MONO), C-reactive protein (CRP), albumin (ALB), neutrophil-to-lymphocyte ratio (NLR, NLR=NEUT/LYM), lymphocyte-to-monocyte ratio (LMR, LMR=LYM/MONO), platelet-to-lymphocyte ratio (PLR, PLR=PLT/LYM), systemic immune-inflammation index (SII, SII=PLT × NEUT/LYM), systemic inflammation response index (SIRI, SIRI=NEUT × MONO/LYM), and C-reactive protein-to-albumin ratio (CAR, CAR=CRP/ALB). The laboratory data were all collected before the first treatment to ensure they reflect the baseline immune and inflammatory status prior to treatment.

Definition of recurrence

In this study, recurrence is defined as the pathological or radiological confirmation of tumor regrowth or metastasis at the primary tumor site or in distant organs during postoperative follow-up. The diagnostic criteria for recurrence: clinical recurrence (emergence of symptoms like pain, swelling, or difficulty swallowing), radiological recurrence (evidence of tumor reappearance or growth through imaging techniques, such as CT, MRI, or ultrasound), and pathological recurrence (confirmed by histological examination through biopsy or surgical resection showing regrowth of tumor cells). Patients were considered as having recurrence if any of the above signs are observed during follow-up; those without recurrence were defined as having no tumor recurrence or metastasis during the follow-up period [11].

Follow-up definition

As of May 2024, recurrence data were collected primarily through electronic medical records to assess patients recurrence status. Due to the lack of precise recurrence dates provided by most patients, specific recurrence dates of recurrence could not be obtained. Therefore, the collected recurrence information only covers data up to May 2024.

Machine learning models

To explore recurrence-associated factors in early-stage TSCC, three machine learning methods were employed (Least Absolute Shrinkage and Selection Operator [LASSO], Extreme Gradient Boosting [Xgboost], and Support Vector Machine [SVM]). Of them, LASSO applies L1 penalty terms for variable selection and regularization, which helps to improve model interpretability. Xgboost is a gradient boosting decision tree-based integrated learning method, capable of effectively handling missing data and automatically learning feature combinations. SVM is a supervised learning method that distinguishes samples of different categories by determining the optimal decision boundary. These three methods, each with their unique characteristics, were applied together to select features related to TSCC recurrence risk, in order to construct a risk prediction model with high accuracy and strong interpretability.

Statistical analyses

SPSS26.0 software was used to process and analyze the collected data. Categorical variables, expressed as rates (%), were analyzed using chi-square tests. The Kolmogorov-Smirnov test was initially applied to assess the distribution of continuous variables. For normally distributed variables, data were presented as mean ± standard deviation (Mean ± SD), and independent sample t-tests were adopted for group comparisons. Non-normally distributed variables were described in the form of quartiles (P50 [P25, P75]) and analyzed using the rank-sum test.

Further statistical analyses were performed using R software version 4.2.2. Cox regression modeling was conducted using the “coxph” function from the survival package to assess model performance. LASSO regression modeling was implemented using the “glmnet” package, SVM modeling with the “kernlab” package, and Xgboost modeling with the “Xgboost” package. Decision curve analysis (DCA) was visualized using the “rmda” package, and receiver operating characteristic (ROC) curves were

Table 1. Comparison of baseline data between recurrence and non-recurrence groups

Factors	Recurrence group (n=160)	Non-recurrence group (n=355)	χ^2	P
Age				
≥50 years old	67 (41.88%)	146 (41.13%)	0.025	0.873
<50 years old	93 (58.13%)	209 (58.87%)		
Gender				
Male	45 (28.12%)	98 (27.61%)	0.015	0.903
Female	115 (71.88%)	257 (72.39%)		
Pathological classification				
High differentiation	114 (71.25%)	308 (86.76%)	17.931	<0.001
Low + moderate differentiation	46 (28.75%)	47 (13.24%)		
Tumor location				
Anterior one-third of the tongue	16 (10.00%)	57 (16.06%)	13.628	0.001
Middle one-third of the tongue	104 (65.00%)	253 (71.27%)		
Posterior one-third of the tongue	40 (25.00%)	45 (12.68%)		
Tumor diameter				
≤3 cm	109 (68.12%)	304 (85.63%)	21.287	<0.001
≥3 cm	51 (31.87%)	51 (14.37%)		
Use of radiotherapy				
With	126 (78.75%)	279 (78.59%)	0.002	0.968
Without	34 (21.25%)	76 (21.41%)		
Use of chemotherapy				
With	111 (69.38%)	303 (85.35%)	17.858	<0.001
Without	49 (30.63%)	52 (14.65%)		
WBC ($\times10^9$/L)	6.28 [5.87, 6.78]	6.51 [5.84, 7.41]	3.077	0.002
PLT ($\times10^9$/L)	187.12±9.95	195.22±10.88	8.030	<0.001
NEUT ($\times10^9$/L)	4.53 [4.27, 4.72]	4.28 [3.93, 4.61]	5.632	<0.001
LYM ($\times10^9$/L)	1.94 [1.69, 2.42]	2.44 [2.13, 2.75]	7.521	<0.001
MONO ($\times10^9$/L)	0.43 [0.25, 0.61]	0.44 [0.28, 0.68]	1.088	0.277
CRP (mg/L)	15.52 [13.79, 17.59]	13.98 [11.59, 16.12]	5.425	<0.001
ALB (g/L)	38.00 [34.00, 41.00]	40.00 [37.00, 44.00]	5.080	<0.001
NLR	2.23 [1.87, 2.80]	1.78 [1.51, 2.06]	9.193	<0.001
LMR	4.85 [3.34, 7.97]	5.11 [3.52, 9.20]	1.837	0.066
PLR	43.54 [36.10, 49.48]	38.46 [33.99, 46.35]	3.911	<0.001
SII	195.07 [160.16, 229.28]	167.63 [141.75, 201.50]	5.595	<0.001
SIRI	0.92 [0.51, 1.40]	0.82 [0.46, 1.23]	2.648	0.008
CAR	0.40 [0.34, 0.47]	0.33 [0.29, 0.40]	6.936	<0.001

Note: WBC: White Blood Cell Count, PLT: Platelet Count, NEUT: Neutrophil Count, LYM: Lymphocyte Count, MONO: Monocyte Count, CRP: C-reactive Protein, ALB: Albumin, NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, CAR: C-reactive Protein-to-Albumin Ratio.

plotted with the "rocr" package. A *P*-value of <0.05 was considered statistically significant.

Results

Patient baseline data

A comparison of baseline characteristics between the recurrence and non-recurrence groups revealed no statistically significant differences in age, gender, radiotherapy use, or MONO (all P>0.05, **Table 1**). Significant differences were observed in pathological classification, tumor location, tumor diameter, and chemotherapy use (all P<0.001). In terms of laboratory parameters, WBC, NEUT, LYM, PLT, CRP, ALB, NLR, PLR, SII, SIRI, and CAR differed significantly between groups (all P<0.01). LMR

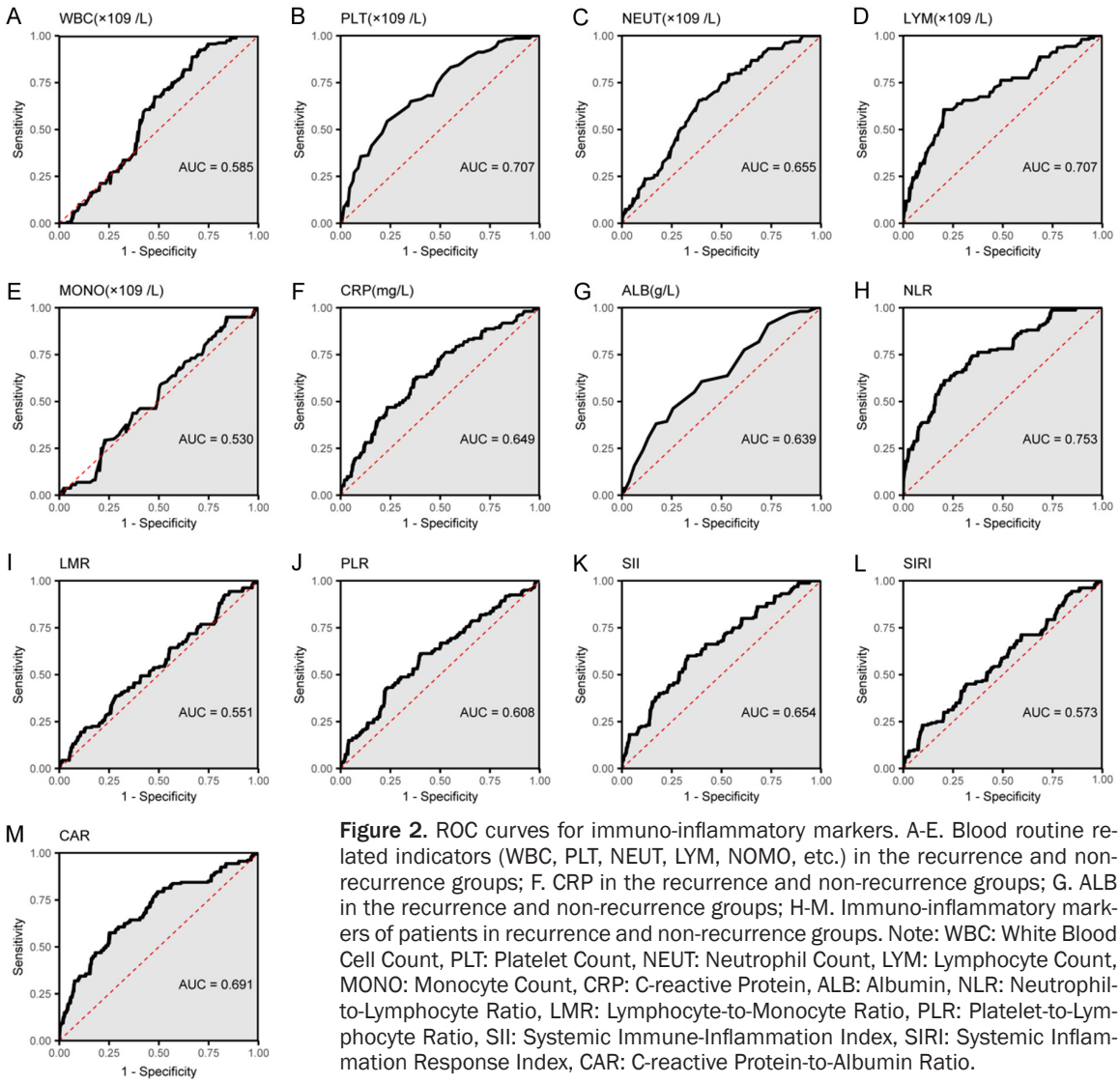

Figure 2. ROC curves for immuno-inflammatory markers. A-E. Blood routine related indicators (WBC, PLT, NEUT, LYM, NOMO, etc.) in the recurrence and non-recurrence groups; F. CRP in the recurrence and non-recurrence groups; G. ALB in the recurrence and non-recurrence groups; H-M. Immuno-inflammatory markers of patients in recurrence and non-recurrence groups. Note: WBC: White Blood Cell Count, PLT: Platelet Count, NEUT: Neutrophil Count, LYM: Lymphocyte Count, MONO: Monocyte Count, CRP: C-reactive Protein, ALB: Albumin, NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, CAR: C-reactive Protein-to-Albumin Ratio.

showed no significant difference (P=0.066), suggesting a borderline association.

Patient grouping for validation and training sets

To validate the model, patients were randomly assigned into a validation set and a training set in a 66%:34% ratio. Due to the inclusion of both categorical and continuous variables in this study, continuous variables were transformed for data consistency. ROC curves were generated (**Figure 2**), and cut-off values were determined as nodes (**Table 2**) from binary classification of the continuous variables. Subsequently, a further baseline data comparison was made between validation and training sets, revealing no statistical inter-group differences, indicating comparability (P>0.05, **Table 3**).

Screening and evaluation of feature variables by the three models

In this study, LASSO, Xgboost, and SVM were used to select recurrence-related feature variables (**Figure 3**). The LASSO model identified 14 feature variables, including WBC, PLT, NEUT, MONO, LYM, CRP, ALB, NLR, SIRI, CAR, pathological classification, tumor diameter, chemotherapy use, and tumor location (**Figure 4A**). Xgboost identified 19 feature variables, including LYM, NLR, CAR, SII, PLT, WBC, CRP, NEUT, ALB, tumor location, tumor diameter, chemotherapy use, pathological classification, SIRI, MONO, LMR, radiotherapy, age, and gender

Table 2. ROC curve parameters of immuno-inflammatory markers

Predictor	AUC	95% CI	Cut-off	Sensitivity	Specificity	Accuracy	Youden index
WBC (×10^9/L)	0.585	0.536-0.634	7.275	29.58%	92.50%	50.87%	22.08%
PLT (×10^9/L)	0.707	0.660-0.755	187.5	76.62%	54.37%	30.29%	30.99%
NEUT (×10^9/L)	0.655	0.606-0.704	4.405	61.13%	65.62%	62.52%	26.75%
LYM (×10^9/L)	0.707	0.657-0.757	2.035	79.72%	60.62%	26.21%	40.34%
MONO (×10^9/L)	0.53	0.478-0.582	0.855	16.06%	95.00%	59.42%	11.06%
CRP (mg/L)	0.649	0.598-0.700	14.815	63.38%	61.88%	62.91%	25.26%
ALB (g/L)	0.639	0.588-0.690	35.5	82.82%	38.12%	31.07%	20.94%
NLR	0.753	0.708-0.798	2.111	79.44%	61.25%	73.79%	40.69%
LMR	0.551	0.497-0.604	3.857	71.83%	38.75%	38.45%	10.58%
PLR	0.608	0.554-0.661	41.236	60.00%	61.25%	60.39%	21.25%
SII	0.654	0.603-0.705	187.072	67.04%	60.00%	64.85%	27.04%
SIRI	0.573	0.519-0.627	1.617	90.42%	23.12%	69.51%	13.55%
CAR	0.691	0.640-0.742	0.395	74.93%	57.50%	69.51%	32.43%

Note: WBC: White Blood Cell Count, PLT: Platelet Count, NEUT: Neutrophil Count, LYM: Lymphocyte Count, MONO: Monocyte Count, CRP: C-reactive Protein, ALB: Albumin, NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, CAR: C-reactive Protein-to-Albumin Ratio.

(**Figure 4B**). SVM also identified 19 feature variables, including LYM, NLR, CAR, SII, PLT, WBC, CRP, NEUT, ALB, tumor location, tumor diameter, chemotherapy use, pathological classification, SIRI, MONO, LMR, radiotherapy use, age, and gender (**Figure 4C**).

Screening of feature variables and construction of a nomogram model

The performance of three models were compared using the Delong test, and the results showed that both Xgboost and SVM demonstrated consistent efficacy in predicting patient recurrence (**Figure 4D-F**). Therefore, we used a Venn diagram to screen common factors between the two models, identifying 19 identical feature variables (**Figure 5A**). Subsequently, correlation analysis was conducted to explore the linear relationships between these features. Strong correlations were identified among LYM, MONO, ALB, LMR, PLR, and several other indicators, prompting the exclusion of these correlated variables (**Figure 5B** and **5C**).

Cox regression analysis evaluated risk factors for TSCC recurrence. Univariate analysis identified significant associations (P<0.05) with WBC (<7.275 vs. ≥7.275, HR=6.491, P<0.001), PLT (<187.500 vs. ≥187.500, HR=2.627, P<0.001), NEUT (<4.405 vs. ≥4.405, HR=0.443, P< 0.001), CRP (<14.815 vs. ≥14.815, HR=0.456, P<0.001), NLR (<2.111 vs. ≥2.111, HR=0.216, P<0.001), SII (<187.072 vs. ≥187.072, HR= 0.364, P<0.001), SIRI (<1.617 vs. ≥1.617, HR=0.472, P<0.001), CAR (<0.395 vs. ≥0.395, HR=0.343, P<0.001), pathological differentiation (low/moderate vs. high, HR=2.216, P< 0.001), tumor diameter (≥3 cm vs. ≤3 cm, HR=2.205, P<0.001), chemotherapy (no vs. yes, HR=2.039, P<0.001), and tumor location (middle one-third vs. anterior one-third, HR= 2.516, P=0.030; posterior one-third vs. anterior one-third, HR=4.735, P<0.001). Multivariate analysis confirmed significant associations (P<0.05) for WBC (HR=5.184, P<0.001), PLT (HR=1.967, P=0.001), NEUT (HR=0.624, P= 0.030), CRP (HR=0.635, P=0.034), NLR (HR= 0.202, P<0.001), CAR (HR=0.489, P<0.001), pathological differentiation (HR=2.904, P< 0.001), chemotherapy (HR=1.864, P=0.008), and posterior one-third tumor location (HR= 2.810, P=0.030). SII (P=0.133), SIRI (P=0.097), tumor diameter (P=0.663), and middle one-third tumor location (P=0.090) were not significant in multivariate analysis (**Table 4**).

The Cox multivariate analysis further identified several independent predictors for recurrence: WBC (HR=5.184, P<0.001), PLT (HR=1.967, P=0.001), NLR (HR=0.202, P<0.001), CAR (HR=0.489, P<0.001), pathological differentiation (low/moderate vs. high differentiation,

Table 3. Comparison of baseline data between validation set and training set samples

Factors	Validation set (n=339)	Training set (n=176)	χ^2	*P*
Age				
≥50 years old	142 (41.89%)	71 (40.34%)	0.114	0.735
<50 years old	197 (58.11%)	105 (59.66%)		
Gender				
Male	90 (26.55%)	53 (30.11%)	0.734	0.392
Female	249 (73.45%)	123 (69.89%)		
Pathological classification				
High differentiation	280 (82.60%)	142 (80.68%)	0.287	0.592
Low + moderate differentiation	59 (17.40%)	34 (19.32%)		
Tumor location				
Anterior one-third of the tongue	43 (12.68%)	30 (17.05%)	2.364	0.307
Middle one-third of the tongue	242 (71.39%)	115 (65.34%)		
Posterior one-third of the tongue	54 (15.93%)	31 (17.61%)		
Tumor diameter				
≤3 cm	272 (80.24%)	141 (80.11%)	0.001	0.974
≥3 cm	67 (19.76%)	35 (19.89%)		
Use of radiotherapy				
With	267 (78.76%)	138 (78.41%)	0.009	0.926
Without	72 (21.24%)	38 (21.59%)		
Use of chemotherapy				
With	275 (81.12%)	139 (78.98%)	0.338	0.561
Without	64 (18.88%)	37 (21.02%)		
WBC ($\times 10^9$/L)				
≥7.275	80 (23.60%)	37 (21.02%)	0.438	0.508
<7.275	259 (76.40%)	139 (78.98%)		
PLT ($\times 10^9$/L)				
≥187.500	223 (65.78%)	122 (69.32%)	0.655	0.418
<187.500	116 (34.22%)	54 (30.68%)		
NEUT ($\times 10^9$/L)				
≥4.405	170 (50.15%)	73 (41.48%)	3.495	0.062
<4.405	169 (49.85%)	103 (58.52%)		
LYM ($\times 10^9$/L)				
≥2.035	231 (68.14%)	115 (65.34%)	0.412	0.521
<2.035	108 (31.86%)	61 (34.66%)		
MONO ($\times 10^9$/L)				
≥0.855	43 (12.68%)	22 (12.50%)	0.004	0.952
<0.855	296 (87.32%)	154 (87.50%)		
CRP (mg/L)				
≥14.815	154 (45.43%)	75 (42.61%)	0.372	0.542
<14.815	185 (54.57%)	101 (57.39%)		
ALB (g/L)				
≥35.500	256 (75.52%)	137 (77.84%)	0.346	0.556
<35.500	83 (24.48%)	39 (22.16%)		
NLR				
≥2.111	107 (31.56%)	64 (36.36%)	1.204	0.273
<2.111	232 (68.44%)	112 (63.64%)		

LMR				
≥3.856	226 (66.67%)	127 (72.16%)	1.621	0.203
<3.856	113 (33.33%)	49 (27.84%)		
PLR				
≥41.236	160 (47.20%)	80 (45.45%)	0.141	0.707
<41.236	179 (52.80%)	96 (54.55%)		
SII				
≥187.072	140 (41.30%)	73 (41.48%)	0.002	0.969
<187.072	199 (58.70%)	103 (58.52%)		
SIRI				
≥1.617	47 (13.86%)	24 (13.64%)	0.005	0.943
<1.617	292 (86.14%)	152 (86.36%)		
CAR				
≥0.395	128 (37.76%)	57 (32.39%)	1.452	0.228
<0.395	211 (62.24%)	119 (67.61%)		

Note: WBC: White Blood Cell Count, PLT: Platelet Count, NEUT: Neutrophil Count, LYM: Lymphocyte Count, MONO: Monocyte Count, CRP: C-reactive Protein, ALB: Albumin, NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, CAR: C-reactive Protein-to-Albumin Ratio.

HR=2.904, P<0.001), chemotherapy (no vs. yes, HR=1.864, P=0.008), and posterior one-third tumor location (HR=2.810, P=0.030). Notably, SII, SIRI, and middle one-third tumor location, which were significant in univariate analysis, did not reach clinical significance in multivariate modeling (all P>0.05). Tumor diameter (≥3 cm) also showed no significant association with recurrence in multivariate analysis (HR=1.102, P=0.663). Additionally, age, gender, and radiotherapy were not significantly associated with recurrence. These results highlight the importance of inflammatory markers (e.g., WBC, PLT, NLR, CAR), pathological features, and treatment choices in determining recurrence risk. The nomogram model achieved a C-index of 0.902 (0.866-0.937), and the goodness-of-fit test showed no statistical difference (P=0.621), indicating that this model has high clinical value.

Validation of the performance of the nomogram model

In the final part of our study, we comprehensively evaluated the nomogram's accuracy (ROC curves), calibration (calibration plots), and clinical utility (DCA curves). In the training set, the nomogram achieved an AUC of 0.902, demonstrating excellent discrimination (**Figure 6A**). The calibration plots showed the model's predicted probabilities matched well with the observed probabilities, indicating high calibration (**Figure 6B**). DCA revealed a net benefit rate of 32.15% across most threshold values, demonstrating net clinical benefit in predicting patient recurrence (**Figure 6C**). In the validation set, the nomogram model achieved an AUC of 0.819, confirming its external validation capability (**Figure 6D**). Although the AUC in the validation set was slightly lower than that in the training set, it still indicated acceptable discrimination in an independent dataset. The calibration plot for the validation set further confirmed the model's consistent predictive performance (**Figure 6E**). DCA in the validation set showed a net benefit rate of 71.02%, highlighting the nomogram's positive decision support for clinical decision-making across a wide range of predefined risk thresholds (**Figure 6F**).

Comparison of training group model and peripheral blood cell ratio in predicting patient recurrence

Statistical comparison using the DeLong test revealed that the nomogram demonstrated superior predictive performance for patient relapse compared to peripheral blood cell ratios, with significant differences observed between their ROC curves. The analysis revealed that several markers, such as NLR, LMR, PLR, SII, SIRI, and CAR, exhibited substantial differences compared to the Risk1 model (P<0.001), indicating that the nomogram model provided superior predictive accu-

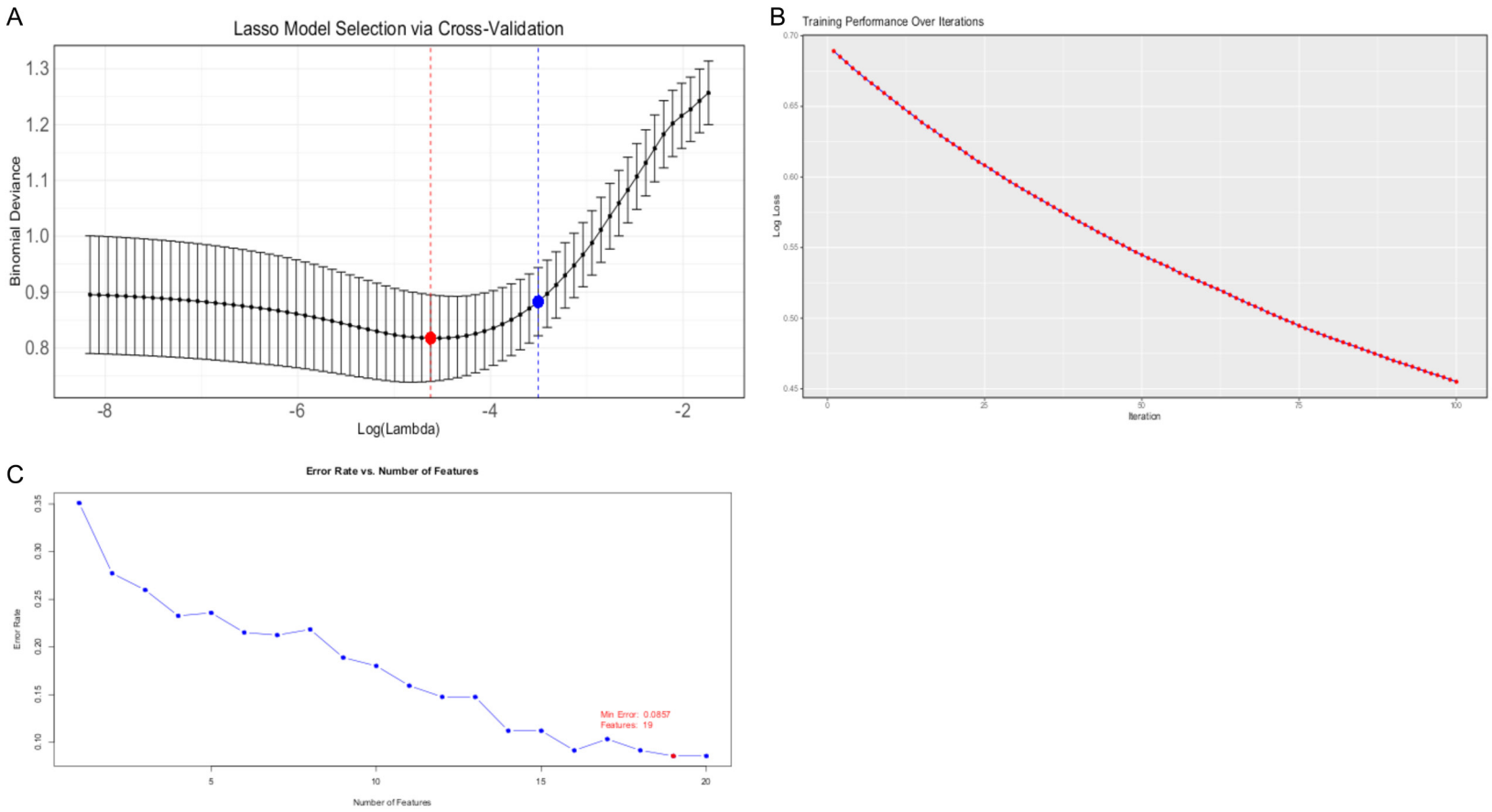

Figure 3. Model coefficient screening using LASSO, Xgboost, and SVM. A. Screening of feature variables by LASSO model, with red dots representing minimum value and blue dots representing 1se value; B. Xgboost model training process; C. Feature variable screening by SVM, with 19 feature variables found when minimum error =0.2459. Note: LASSO: Least Absolute Shrinkage and Selection Operator, Xgboost: Extreme Gradient Boosting, SVM: Support Vector Machine.

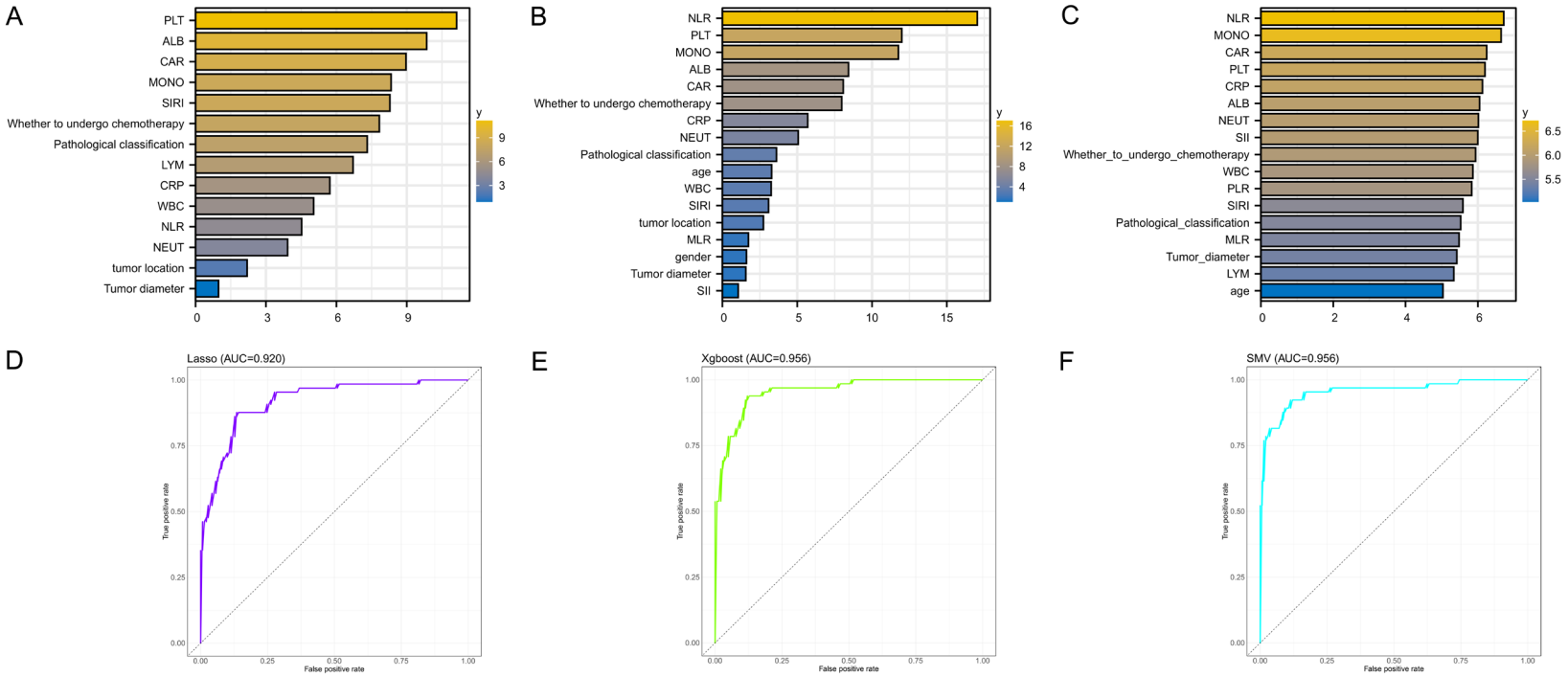

Figure 4. Feature variables and ROC curves for the three models. A-C. Feature variables identified by LASSO, Xgboost, and SVM models; D-F. ROC curves for LASSO, Xgboost, and SVM models. Note: WBC: White Blood Cell Count, PLT: Platelet Count, NEUT: Neutrophil Count, LYM: Lymphocyte Count, MONO: Monocyte Count, CRP: C-reactive Protein, ALB: Albumin, NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, CAR: C-reactive Protein-to-Albumin Ratio, LASSO: Least Absolute Shrinkage and Selection Operator, Xgboost: Extreme Gradient Boosting, SVM: Support Vector Machine, ROC: Receiver Operating Characteristic.

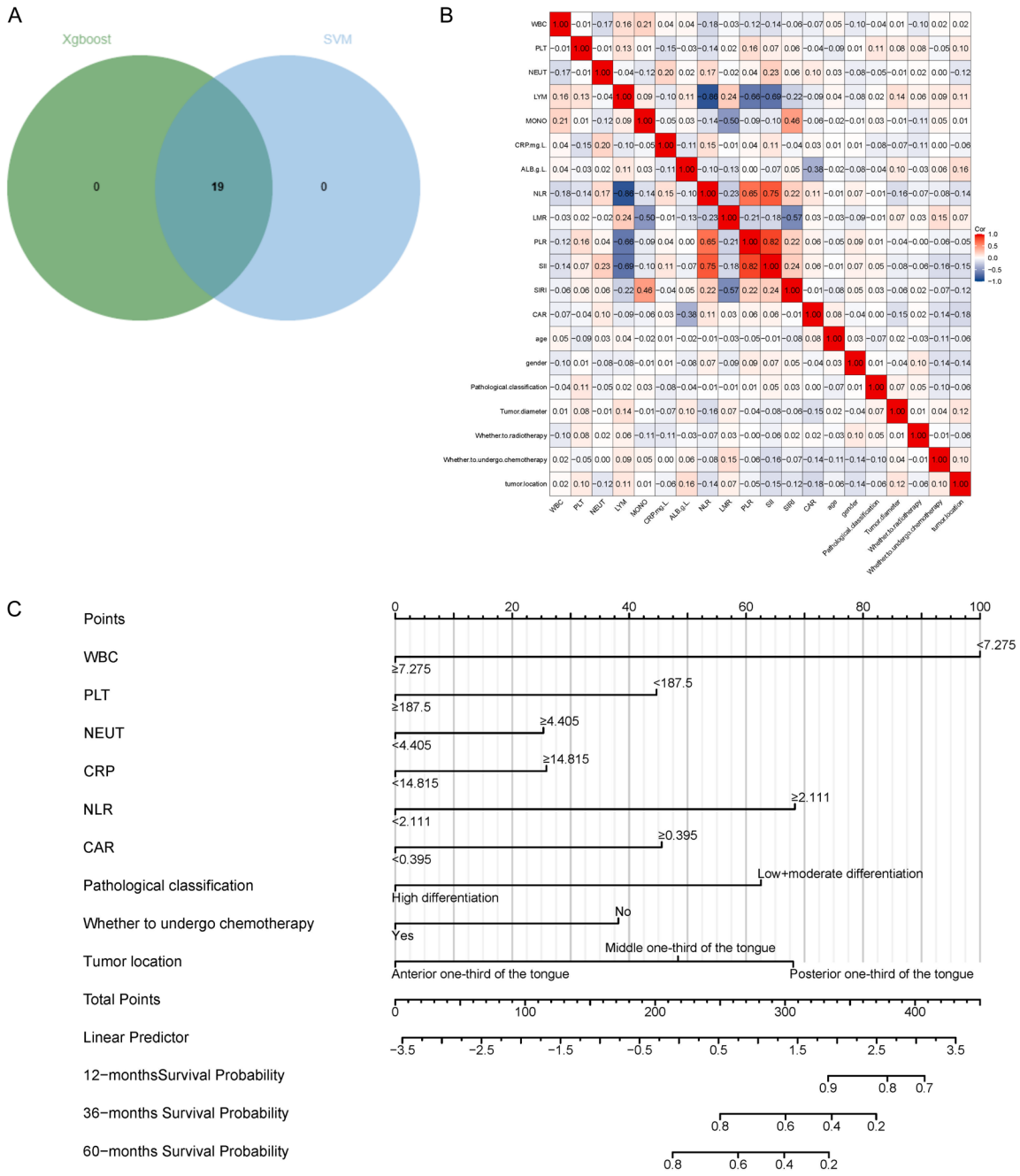

Figure 5. Common feature variable selection and Nomogram model construction. A. Venn diagram screening for common variables of Xgboost and SMV in predicting recurrence in patients; B. Heat map of the correlation; C. Nomogram model construction for recurrence risk. Note: WBC: White Blood Cell Count, PLT: Platelet Count, NEUT: Neutrophil Count, LYM: Lymphocyte Count, MONO: Monocyte Count, CRP: C-reactive Protein, ALB: Albumin, NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, CAR: C-reactive Protein-to-Albumin Ratio, Xgboost: Extreme Gradient Boosting, SVM: Support Vector Machine, ROC: Receiver Operating Characteristic.

racy. This suggests that the nomogram model provides a more reliable and accurate prediction of recurrence compared to peripheral blood cell ratios (**Table 5**).

Discussion

Among oral cavity malignancies, TSCC stands out for its aggressive behavior and adverse

Table 4. Cox regression analysis of predictive factors for recurrence in TSCC patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
WBC				
≥7.275	Reference		Reference	
<7.275	6.491 (2.849-14.787)	<0.001	5.184 (2.235-12.025)	<0.001
PLT				
≥187.500	Reference		Reference	
<187.500	2.627 (1.802-3.829)	<0.001	1.967 (1.298-2.982)	0.001
NEUT				
≥4.405	Reference		Reference	
<4.405	0.443 (0.298-0.659)	<0.001	0.624 (0.407-0.956)	0.030
CRP				
≥14.815	Reference		Reference	
<14.815	0.456 (0.310-0.671)	<0.001	0.635 (0.417-0.967)	0.034
NLR				
≥2.111	Reference		Reference	
<2.111	0.216 (0.147-0.318)	<0.001	0.202 (0.086-0.472)	<0.001
SII				
≥187.072	Reference		Reference	
<187.072	0.364 (0.247-0.535)	<0.001	1.931 (0.818-4.558)	0.133
SIRI				
≥1.617	Reference		Reference	
<1.617	0.472 (0.302-0.738)	<0.001	0.658 (0.401-1.079)	0.097
CAR				
≥0.395	Reference		Reference	
<0.395	0.343 (0.234-0.503)	<0.001	0.489 (0.328-0.729)	<0.001
Age				
≥50 years old	Reference			
<50 years old	0.868 (0.595-1.267)	0.463		
Gender				
Male	Reference			
Female	0.874 (0.576-1.324)	0.524		
Pathological classification				
High differentiation	Reference		Reference	
Low + moderate differentiation	2.216 (1.455-3.376)	<0.001	2.904 (1.811-4.658)	<0.001
Tumor diameter				
≤3 cm	Reference		Reference	
≥3 cm	2.205 (1.475-3.298)	<0.001	1.102 (0.712-1.706)	0.663
Whether to radiotherapy				
Yes	Reference			
No	0.808 (0.497-1.312)	0.388		
Whether to undergo chemotherapy				
Yes	Reference		Reference	
No	2.039 (1.349-3.080)	<0.001	1.864 (1.176-2.956)	0.008
Tumor location				
Anterior one-third of the tongue	Reference		Reference	
Middle one-third of the tongue	2.516 (1.096-5.777)	0.030	2.112 (0.891-5.008)	0.090
Posterior one-third of the tongue	4.735 (1.954-11.473)	<0.001	2.810 (1.102-7.163)	0.030

Note: TSCC: Tongue Squamous Cell Carcinoma, WBC: White Blood Cell Count, PLT: Platelet Count, NEUT: Neutrophil Count, CRP: C-reactive Protein, NLR: Neutrophil-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, CAR: C-reactive Protein-to-Albumin Ratio.

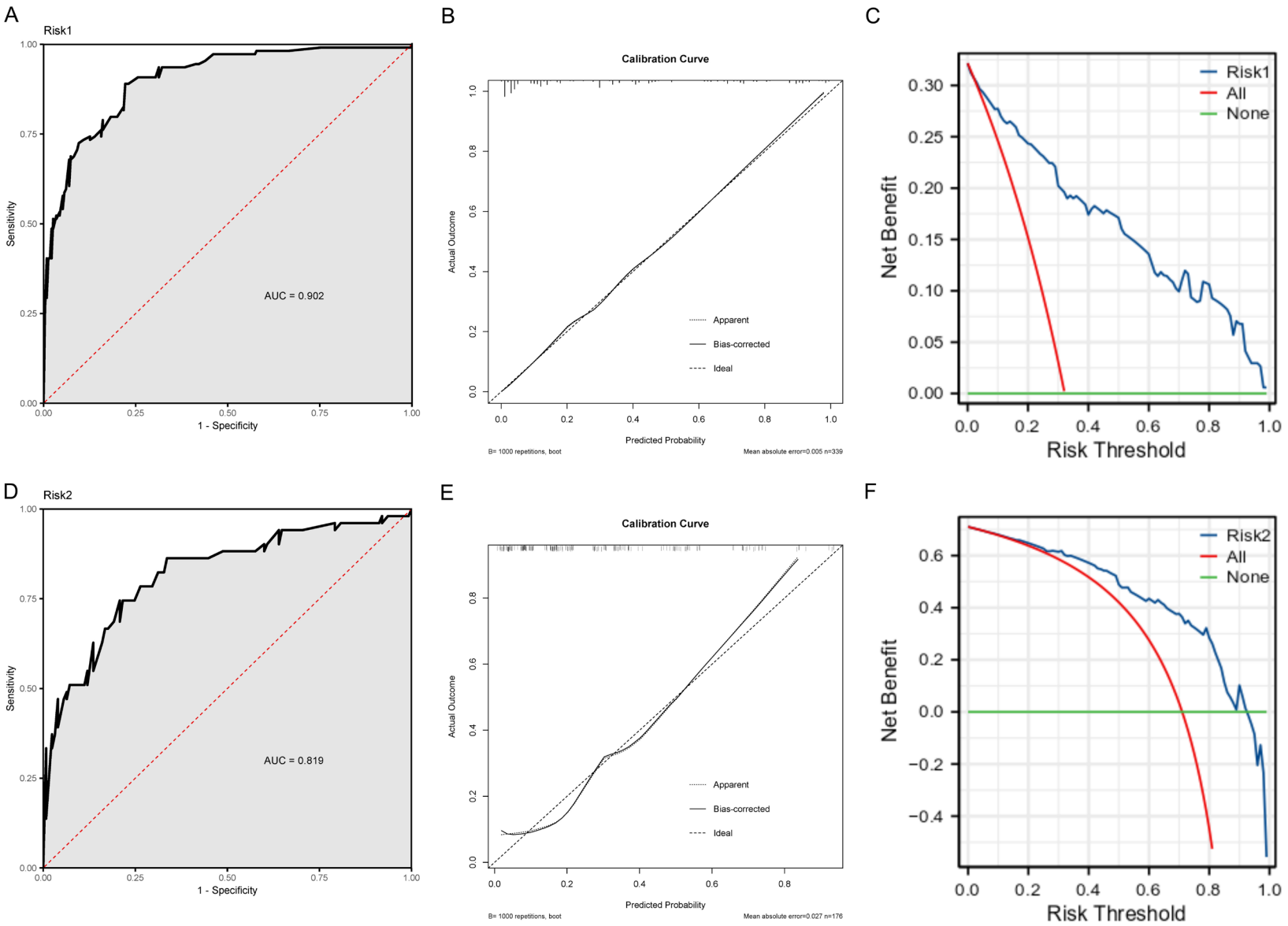

Figure 6. Performance validation of the Nomogram model. A. ROC curve of the Nomogram model for predicting patient recurrence in the training set; B. Calibration curve of the Nomogram model in the training set; C. DCA curve of the Nomogram model in the training set; D. ROC curve of Nomogram model for predicting patient recurrence in the validation set; E. Calibration curve of the Nomogram model in the validation set; F. DCA curve of the Nomogram model in the validation set. Note: ROC: Receiver Operating Characteristic, DCA: Calibration Curve, Decision Curve Analysis.

Table 5. Comparison of AUC values between nomogram model and peripheral blood cell ratios

Marker 1	Marker 2	Z_value	*P*_value	AUC_difference	CI_lower_upper
NLR	Risk1	-3.966	<0.001	-0.138	-0.206 - -0.070
LMR	Risk1	-9.264	<0.001	-0.365	-0.443 - -0.288
PLR	Risk1	-6.864	<0.001	-0.269	-0.346 - -0.192
SII	Risk1	-6.258	<0.001	-0.235	-0.309 - -0.161
SIRI	Risk1	-8.742	<0.001	-0.345	-0.422 - -0.267
CAR	Risk1	-5.477	<0.001	-0.203	-0.275 - -0.130

Note: NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, CAR: C-reactive Protein-to-Albumin Ratio.

prognosis [14, 15]. Current clinical practice relies heavily on TNM staging for prognostic evaluation and therapeutic decision-making [16]. However, prognostic evaluation in early-stage disease presents significant challenges, as tumor heterogeneity and biological complexity often exceed the discriminative capacity of conventional staging criteria [17]. This study aims to develop and validate novel prognostic factors that, when combined with standard TNM staging, can refine risk stratification for early TSCC management.

First, this investigation utilized a tri-model machine learning framework (LASSO, XGBoost, SVM) for recurrence factor identification in TSCC. The LASSO method selected 14 key predictors, while both Xgboost and SVM identified 19 relevant features. Performance evaluation using ROC curves showed exceptional accuracy for both XGBoost and SVM models (AUC= 0.902), underscoring their effectiveness in detecting recurrence-related characteristics. This analysis confirms that Xgboost and SVM algorithms exhibit greater comprehensiveness in identifying recurrence-related variables, showcasing their advanced pattern recognition capacity for detecting intricate recurrence-associated signatures in TSCC patients. Given the superior predictive performance and consistent results from both Xgboost and SVM models, we employed the overlapping feature sets identified by these algorithms for subsequent Cox regression analysis. This approach enabled the precise identification of key prognostic factors independently associated with recurrence risk in early-stage TSCC patients [18]. By combining the strengths of both high-performing algorithms with rigorous statistical verification, a nomogram was generated, offering enhanced precision, clarity, and clinical utility [19]. It was found that PLT pathological classification, and chemotherapy use were independent risk factors for TSCC recurrence. Elevated PLT may provide a favorable environment for tumor growth and spread, increasing the risk of recurrence [20]. High CRP levels reflect an inflammatory state, which is associated with tumor aggressiveness and poor prognosis [21]. Low ALB levels suggest malnutrition, which can negatively impact therapeutic effectiveness [22]. Previously, Han et al. matched data of 97 patients with recurrent hepatocellular carcinoma after transplantation by propensity scores and found that elevated PLT ($\geq 75\times10^9$/L) was associated with a 1.9-fold increased risk of disease recurrence compared to patients with lower PLT levels [23]. In addition, Kolehmainen et al. pointed out that PLT is a significant prognostic indicator for recurrent endometrial carcinoma [24]. CAR, as a comprehensive index, reflects inflammation and nutritional status and is closely linked to tumor progression and treatment responsiveness, which is an important factor in predicting recurrence. For example, Bekki et al. found that preoperative CAR is an independent predictor of long-term outcomes in stage I-III colorectal cancer following curative surgery [25]. In addition, Namikawa et al. established a clear association between increased CAR values and unfavorable survival outcomes in unresectable and recurrent gastric cancer [26]. Pathological grading refers to the degree of tumor differentiation, with poorly differentiated tumors having a higher recurrence risk due to their greater invasiveness and metastasis potential. Okada et al. [27] highlighted the close correlation between histological malignancy grading of TSCC and cervical lymph node metastases, finding that poorly differentiated TSCC was more likely to develop cervical lymph node metastases. Similarly, Wu et al. [28] emphasized the significant role of tumor pathological classification in predicting cervical lymph node metastatic risk in early-stage TSCC. At present, adjuvant chemotherapy remains one of the primary treatment options for TSCC. Yanamoto et

al. [29] further confirmed that adjuvant chemotherapy effectively reduced recurrence rate, providing new hope for TSCC patients. Combining these factors, we can more comprehensively evaluate the recurrence risk in TSCC patients, formulate individualized treatment plans, and improve their prognostic outcomes through continuous monitoring and adjustment of treatment strategies.

At the end of the study, we comprehensively evaluated the Nomogram's accuracy, calibration, and clinical value in predicting the recurrence of patients with early-stage TSCC by using ROC, calibration, and DCA. The model demonstrated excellent discriminative ability, with AUC values of 0.902 in the training set and 0.819 in the validation set. The calibration plot further confirmed reliable predictive consistency. Moreover, DCA curve analysis indicated that the model provides significant net benefits for clinical decision-making. This study used Cox regression for model construction instead of directly using Xgboost and SVM. This choice was made because Cox regression provides clear probability outputs and risk factor weights, which are easy to interpret and apply in clinical practice. Compared with the complexity and black-box characterization of Xgboost and SVM, Cox regression is of greater significance for clinical decision-making, providing physicians with intuitive and practical risk assessment tools to help formulate treatment plans that are more in line with the patient's actual situation [30, 31]. A related machine learning approach was adopted by Fatapour et al. [14], where the SEER database served as the primary data source for developing an oral TSCC recurrence prediction tool. In their study, the Gradient Boosting Machine (GBM) model achieved an AUC of 0.75 for 5-year predictions and 0.74 for 10-year predictions, with a precision of 97.7% for 5-year prediction and 94.0% for 10-year prediction. While their model showed promising results, our nomogram achieved higher AUC values (AUC= 0.902 for training and 0.819 for validation). Notably, both approaches incorporated comparable clinical parameters, including tumor history, patient age, and tumor histology, which also highlights the importance of integrating multiple risk factors for improved recurrence prediction [14].

However, this study is restricted by limited samples and reliance on retrospective data, which may affect the wide applicability and accuracy of the findings. The study's statistical power may be constrained by the limited sample size, while the retrospective nature of the data collection could potentially lead to selection bias, compromising result reliability. Therefore, studies with larger sample sizes will be necessary to further validate the generalizability of the constructed model.

Conclusion

In summary, the developed prediction model for recurrence risk in early-stage TSCC patients based on immuno-inflammatory markers demonstrates strong predictive performance and high clinical applicability, offering a promising tool for personalized treatment strategies.

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Disclosure of conflict of interest

None.

Abbreviations

TSCC, tongue squamous cell carcinoma; OSCC, oral squamous cell carcinoma; LASSO, Least Absolute Shrinkage and Selection Operator; Xgboost, Extreme Gradient Boosting; SVM, Support Vector Machine; WBC, white blood cell count; PLT, platelet count; NEUT, neutrophil count; LYM, lymphocyte count; MONO, monocyte count; CRP, C-reactive protein; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; CAR, C-reactive protein-to-albumin ratio.

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