Cancer Management and Research

Elevate Series

Open Access Full Text Article

ORIGINAL RESEARCH

A Novel Fibrosis-Integrated Nomogram for Predicting Survival in Oral Squamous Cell Carcinoma Patients with Oral Submucous Fibrosis: A Retrospective Cohort Study

Ting Lei[1], Hong Dong[2]

[1]Department of Stomatology, Hubei University of Medicine, Shiyan, Hubei, People's Republic of China; [2]Department of Dental Endodontics, Guoyao Dongfeng Dental Hospital, Shiyan, Hubei, People's Republic of China

Correspondence: Hong Dong, Department of Dental Endodontics, Guoyao Dongfeng Dental Hospital, Shiyan, Hubei, People's Republic of China, Email kqyxyjx@163.com

Background: Oral squamous cell carcinoma (OSCC) with oral submucous fibrosis (OSF) represents a distinct clinicopathological entity with unique prognostic factors not captured by conventional TNM staging. We aimed to develop a fibrosis-integrated nomogram (FIN) for individualized survival prediction in this population.

Methods: We conducted a retrospective cohort study of 314 consecutive OSCC patients with coexisting OSF treated between 2015 and 2022. Patients were randomly divided into training (n=220) and validation (n=94) sets. Independent prognostic factors were identified using Cox regression and integrated into a nomogram predicting 1-year, 3-year, and 5-year overall survival (OS). Model performance was assessed using C-index, time-dependent ROC curves, calibration plots, and decision curve analysis.

Results: Six independent prognostic factors were identified: maximum mouth opening (HR 0.92, P<0.001), areca nut chewing duration >20 years (HR 1.78, P=0.002), N2-3 category (HR 1.89, P=0.001), poor differentiation (HR 1.56, P=0.018), perineural invasion (HR 1.67, P=0.007), and positive surgical margin (HR 2.03, P=0.001). The FIN demonstrated excellent discrimination, with C-indices of 0.79 (95% CI 0.75–0.83) in the training set and 0.77 (95% CI 0.72–0.82) in the validation set, significantly outperforming TNM staging (C-indices 0.68 and 0.66, respectively; both P<0.01). Risk stratification identified three prognostic groups with 5-year OS rates of 78.6%, 48.3%, and 18.9% (log-rank P<0.001).

Conclusion: The fibrosis-integrated nomogram significantly improves survival prediction for OSCC patients with OSF by incorporating simple clinical measures of fibrosis severity and carcinogen exposure, enabling individualized risk assessment.

Keywords: oral squamous cell carcinoma, oral submucous fibrosis, nomogram, survival prediction, areca nut chewing, maximum mouth opening, prognosis

Introduction

Oral squamous cell carcinoma (OSCC) represents the most prevalent malignancy of the oral cavity, accounting for over 90% of oral cancers worldwide.[1] Despite advances in surgical techniques, radiotherapy, and systemic therapy, the 5-year survival rate for OSCC remains approximately 50–60%, with limited improvement observed over the past decades.[2] Notably, a substantial proportion of OSCC cases in specific geographic regions, particularly South and Southeast Asia, arise from oral submucous fibrosis (OSF), a chronic progressive fibrotic disorder of the oral mucosa strongly associated with areca nut chewing.[3,4] OSF is recognized by the World Health Organization as a potentially malignant disorder, with malignant transformation rates ranging from 4% to 7%.[5] The coexistence of OSF and OSCC creates a distinct clinicopathological entity characterized by unique biological behavior and prognostic implications that are not adequately captured by conventional staging systems.[6]

The tumor-node-metastasis (TNM) staging system, currently in its eighth edition, serves as the cornerstone for prognostication and treatment planning in head and neck oncology.[7] However, the TNM system relies exclusively on anatomic extent of disease and fails to incorporate host-related factors, tumor microenvironment characteristics, or

https://doi.org/10.2147/CMAR.S605497
Received: 26 February 2026
Accepted: 11 April 2026
Published: 6 May 2026

etiological exposures that significantly influence patient outcomes.[8] This limitation is particularly evident in OSCC with background OSF, where the fibrotic microenvironment, chronic inflammatory state, and specific carcinogen exposure through areca nut chewing may substantially impact survival independent of tumor stage.[9] Previous studies have demonstrated that OSCC patients with OSF often present with advanced disease yet exhibit distinct patterns of metastasis and treatment response compared to conventional OSCC, suggesting the need for refined prognostic tools.[10,11]

Nomograms, as graphical representations of statistical predictive models, have emerged as valuable tools for individualized risk estimation in oncology.[12] By integrating multiple prognostic variables, nomograms provide more accurate and personalized survival predictions than traditional staging systems. Several prognostic nomograms have been developed for head and neck cancers, incorporating demographic, clinicopathological, and molecular variables.[13,14] However, to our knowledge, no nomogram has been specifically designed for OSCC patients with coexisting OSF, and existing models universally omit OSF-related parameters such as fibrosis severity, mouth opening limitation, and areca nut exposure history.[15] This represents a significant gap in precision oncology for this high-risk population.

The pathophysiology of OSF involves complex interactions between chronic mechanical irritation, areca nut alkaloid-induced fibroblast activation, and collagen deposition mediated by transforming growth factor-β signaling.[16] These processes create a hypoxic, immunosuppressive tumor microenvironment that promotes epithelial-mesenchymal transition, angiogenesis, and therapeutic resistance.[17] Clinically, OSF severity, quantified by maximum mouth opening and clinical staging, correlates with malignant transformation risk and may serve as a surrogate marker for these adverse biological features.[5] Furthermore, prolonged areca nut chewing has been identified as an independent prognostic factor for poor survival in head and neck cancer, likely reflecting both field cancerization effects and treatment resistance mechanisms.[18]

We hypothesized that integrating OSF-specific fibrosis parameters would enhance survival prediction accuracy for OSCC with background OSF. This study developed and validated a novel fibrosis-integrated nomogram (FIN) incorporating maximum mouth opening, areca nut chewing duration, and standard clinicopathological variables. We further compared its predictive performance against the eighth edition AJCC TNM staging system and established risk stratification criteria to guide individualized treatment.

Methods

Study Design and Setting

This retrospective cohort study was conducted at the Department of Dental Endodontics, Guoyao Dongfeng Dental Hospital. Consecutive patients diagnosed with OSCC coexisting with OSF between January 2015 and December 2022 were enrolled. The study protocol was approved by the Institutional Review Board of Guoyao Dongfeng Dental Hospital (Approval No: 2022012151) with waiver of informed consent due to the retrospective design.

Participants

Inclusion criteria comprised: (1) histopathologically confirmed OSCC (ICD-O-3 codes C00-C06, C14.0, and C14.8); (2) preexisting OSF diagnosed histologically by juxtaepithelial hyalinization and chronic inflammation, or clinically by characteristic mucosal blanching and palpable fibrotic bands; (3) curative-intent treatment including radical surgery with or without adjuvant therapy, or definitive chemoradiotherapy; and (4) complete clinicopathological data with minimum follow-up of six months. Exclusion criteria were: distant metastasis at diagnosis; previous malignancies or history of head and neck cancer treatment; synchronous second primary cancers; preoperative antitumor therapy other than neoadjuvant chemotherapy; immunosuppressive therapy or systemic corticosteroid use within three months prior to diagnosis; and missing critical variables exceeding 20%.

Data Collection

Clinical data were extracted from electronic medical records using a standardized case report form through June 30, 2024, ensuring a minimum follow-up duration of six months for all included patients. Demographic variables included age, sex, and body mass index. Lifestyle factors comprised smoking status (never, former, current with pack-years quantification), alcohol consumption, and areca nut chewing history (duration in years, daily frequency, and cumulative

exposure index calculated as years × daily frequency). OSF-related characteristics included maximum mouth opening measured as interincisal distance in millimeters using a standardized Vernier caliper, and OSF clinical stage classified according to the modified Haider classification (Stage I: stomatitis with mucosal changes only; Stage II: fibrotic bands without mouth opening limitation; Stage III: fibrotic bands with interincisal distance 20–35 mm; Stage IV: severe trismus with interincisal distance <20 mm). Tumor characteristics encompassed primary site, T/N category per eighth edition AJCC/UICC TNM staging, histological differentiation, perineural invasion, lymphovascular invasion, and surgical margin status (negative ≥5 mm, close <5 mm, or positive). Treatment modalities and pretreatment laboratory markers (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, hemoglobin) were also recorded.

Outcome Measures

The primary outcome was overall survival, defined as the interval from histopathological diagnosis to death from any cause or last follow-up. The secondary outcome was progression-free survival, defined as the time from diagnosis to first evidence of disease progression (local recurrence, regional recurrence, or distant metastasis) or death from any cause, whichever occurred first. Patients without events were censored at the date of last follow-up.

Sample Size and Missing Data

Sample size was determined based on the principle of ten events per variable for multivariable Cox regression. Anticipating ten to twelve candidate predictors in the final model and assuming a five-year event rate of approximately 45% based on preliminary institutional data, we aimed to include at least 300 patients to ensure adequate statistical power. For variables with missing data below 5%, complete case analysis was employed. For variables with missing data between 5% and 20%, multiple imputation by chained equations was performed with 10 imputations under the assumption of missing at random.

Statistical Analysis

Patients were randomly divided into a training set (70%, n=220) for model development and an internal validation set (30%, n=94) using stratified random sampling by survival status to ensure balanced event distribution. For variables with missing data between 5% and 20%, multiple imputation by chained equations was performed with 10 imputations under the missing-at-random assumption, while variables with <5% missingness were analyzed using complete case analysis. Variable selection proceeded through a three-step approach: first, univariable Cox proportional hazards regression identified variables associated with overall survival ($P < 0.10$); second, to avoid multicollinearity, correlation coefficients between OSF-related variables were examined, and maximum mouth opening was retained over OSF stage due to its higher granularity and continuous nature given the high correlation between these two measures (Spearman's $r = -0.82$); third, significant variables were entered into a multivariable Cox regression using backward elimination based on the likelihood ratio test ($P > 0.05$ for removal) to identify independent prognostic factors, with the proportional hazards assumption verified using Schoenfeld residuals. The FIN was constructed based on the final multivariable model using the rms package, with each variable assigned a weighted score proportional to its regression coefficient and the total score mapped to predicted probabilities of 1-year, 3-year, and 5-year survival. Model discrimination was assessed using Harrell's concordance index with 1000 bootstrap resamples to correct for optimism bias, and time-dependent receiver operating characteristic curves at 1, 3, and 5 years were generated with areas under the curve calculated using the timeROC package. Calibration was evaluated using calibration plots comparing predicted versus observed survival probabilities, with the Hosmer-Lemeshow goodness-of-fit test. Risk stratification was performed by categorizing the total nomogram score into three risk groups using X-tile software version 3.6.1 to determine optimal cut-off values based on minimum P-values from Log rank tests, and Kaplan-Meier survival curves were compared using the Log rank test. Sensitivity analyses were conducted by treatment modality and by excluding patients with follow-up duration <12 months to assess potential immortal time bias, with pre-specified subgroup analyses performed to evaluate nomogram performance across T category, N category, areca nut chewing duration, and maximum mouth opening strata, and interaction tests performed to assess heterogeneity across subgroups. All statistical analyses were performed using R software version 4.3.1, with a two-sided P-value < 0.05 considered statistically significant.

Results

Patient Characteristics

Between January 2015 and December 2022, 342 consecutive patients with OSCC coexisting with OSF were assessed for eligibility. Twenty-eight patients were excluded (distant metastasis, n=8; incomplete follow-up, n=12; previous malignancies, n=5; synchronous second primary cancers, n=3), leaving 314 patients for final analysis. The cohort was randomly divided into a training set (n=220, 70%) and an internal validation set (n=94, 30%), with comparable baseline characteristics between sets (all P>0.05; Table 1).

The median age at diagnosis was 58 years (IQR, 51–65), and 261 patients (83.1%) were male. Areca nut chewing was highly prevalent (n=298, 94.9%), with prolonged exposure common (median duration 18 years, IQR 12–25; >20 years in

Table 1 Baseline Characteristics of Patients in the Training and Validation Sets

Characteristic	Total (n=314)	Training Set (n=220)	Validation Set (n=94)	P-value
Demographics				
Age, years, median (IQR)	58 (51–65)	57 (50–64)	59 (52–66)	0.312
Male sex, n (%)	261 (83.1)	183 (83.2)	78 (83.0)	0.967
BMI, kg/m^2, median (IQR)	22.4 (20.1–24.8)	22.6 (20.3–25.0)	22.1 (19.8–24.5)	0.456
Lifestyle factors				
Smoking, n (%)				0.782
Never	89 (28.3)	61 (27.7)	28 (29.8)	
Former	76 (24.2)	55 (25.0)	21 (22.3)	
Current	149 (47.5)	104 (47.3)	45 (47.9)	
Pack-years, median (IQR)	18 (0–32)	17 (0–31)	20 (0–34)	0.523
Alcohol consumption, n (%)	198 (63.1)	138 (62.7)	60 (63.8)	0.854
Areca nut chewing				
Chewing history, n (%)	298 (94.9)	208 (94.5)	90 (95.7)	0.642
Duration, years, median (IQR)	18 (12–25)	17 (11–24)	19 (13–26)	0.287
Daily frequency, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.634
Cumulative exposure index, median (IQR)	36 (20–60)	34 (18–58)	38 (22–64)	0.412
Duration >20 years, n (%)	128 (40.8)	88 (40.0)	40 (42.6)	0.678
OSF-related characteristics				
Maximum mouth opening, mm, median (IQR)	28 (18–35)	28 (18–35)	27 (17–36)	0.823
Haider OSF stage, n (%)				0.756
I	34 (10.8)	25 (11.4)	9 (9.6)	
II	78 (24.8)	53 (24.1)	25 (26.6)	
III	113 (36.0)	80 (36.4)	33 (35.1)	
IV	89 (28.3)	62 (28.2)	27 (28.7)	
Mucosal blanching severity, n (%)				0.891
None	28 (8.9)	19 (8.6)	9 (9.6)	
Mild	67 (21.3)	48 (21.8)	19 (20.2)	
Moderate	107 (34.1)	74 (33.6)	33 (35.1)	
Severe	112 (35.7)	79 (35.9)	33 (35.1)	
Previous OSF treatment, n (%)	45 (14.3)	32 (14.5)	13 (13.8)	0.856
Tumor characteristics				
Primary site, n (%)				0.723
Buccal mucosa	156 (49.7)	110 (50.0)	46 (48.9)	
Tongue	89 (28.3)	61 (27.7)	28 (29.8)	
Lip	28 (8.9)	20 (9.1)	8 (8.5)	
Gingiva	24 (7.6)	17 (7.7)	7 (7.4)	
Floor of mouth	12 (3.8)	9 (4.1)	3 (3.2)	
Other	5 (1.6)	3 (1.4)	2 (2.1)	

(*Continued*)

https://doi.org/10.2147/CMAR.S605497

Table 1 (Continued).

Characteristic	Total (n=314)	Training Set (n=220)	Validation Set (n=94)	P-value
T category, n (%)				0.812
T1-T2	178 (56.7)	124 (56.4)	54 (57.4)	
T3-T4	136 (43.3)	96 (43.6)	40 (42.6)	
N category, n (%)				0.765
N0-N1	224 (71.3)	156 (70.9)	68 (72.3)	
N2-N3	90 (28.7)	64 (29.1)	26 (27.7)	
AJCC stage, n (%)				0.798
I–II	180 (57.3)	126 (57.3)	54 (57.4)	
III–IV	134 (42.7)	94 (42.7)	40 (42.6)	
Differentiation, n (%)				0.834
Well	98 (31.2)	68 (30.9)	30 (31.9)	
Moderate	142 (45.2)	100 (45.5)	42 (44.7)	
Poor	74 (23.6)	52 (23.6)	22 (23.4)	
Perineural invasion, n (%)	112 (35.7)	78 (35.5)	34 (36.2)	0.902
Lymphovascular invasion, n (%)	89 (28.3)	62 (28.2)	27 (28.7)	0.923
Surgical margin, n (%)				0.876
Negative (≥5 mm)	198 (63.1)	139 (63.2)	59 (62.8)	
Close (<5 mm)	67 (21.3)	46 (20.9)	21 (22.3)	
Positive	49 (15.6)	35 (15.9)	14 (14.9)	
Treatment modalities				
Surgery alone, n (%)	112 (35.7)	78 (35.5)	34 (36.2)	0.902
Surgery + adjuvant RT, n (%)	132 (42.0)	93 (42.3)	39 (41.5)	
Surgery + adjuvant CRT, n (%)	32 (10.2)	22 (10.0)	10 (10.6)	
Definitive CRT, n (%)	38 (12.1)	27 (12.3)	11 (11.7)	
Laboratory markers				
NLR, median (IQR)	2.8 (2.0–4.2)	2.7 (1.9–4.1)	2.9 (2.1–4.5)	0.412
PLR, median (IQR)	142 (108–198)	140 (106–195)	148 (112–205)	0.356
Hemoglobin, g/L, median (IQR)	128 (115–142)	129 (116–143)	126 (113–140)	0.478

Notes: P-values were calculated using χ^2-test, Fisher's exact test, or Mann–Whitney *U*-test as appropriate.
Abbreviations: IQR, interquartile range; BMI, body mass index; OSF, oral submucous fibrosis; RT, radiotherapy; CRT, chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

128 patients [40.8%]). OSF-related characteristics demonstrated substantial functional impairment: median maximum mouth opening was 28 mm (IQR, 18–35), with 89 patients (28.3%) having severe trismus (<20 mm, Haider stage IV) and 112 (35.7%) showing severe mucosal blanching. Tumor characteristics reflected advanced disease in a substantial proportion: the buccal mucosa was the most common primary site (n=156, 49.7%), followed by tongue (n=89, 28.3%); 134 patients (42.7%) presented with AJCC stage III–IV disease. Perineural invasion was identified in 112 cases (35.7%) and lymphovascular invasion in 89 (28.3%). Treatment was predominantly surgical: 276 patients (87.9%) underwent radical resection with neck dissection, of whom 168 (53.5%) received adjuvant radiotherapy and 76 (24.2%) adjuvant chemoradiotherapy. Definitive chemoradiotherapy was administered to 38 patients (12.1%) with unresectable disease or poor surgical candidacy.

Follow-Up and Survival Outcomes

The median follow-up duration was 38 months (IQR, 22–56 months). By the last follow-up date (June 30, 2024), 142 patients (45.2%) had died, and 98 patients (31.2%) had experienced disease progression or recurrence. The 1-year, 3-year, and 5-year overall survival rates were 82.5%, 58.3%, and 48.7%, respectively. The 1-year, 3-year, and 5-year progression-free survival rates were 78.6%, 52.4%, and 43.9%, respectively.

Univariable and Multivariable Survival Analysis

Univariable analysis identified 12 candidate predictors ($P < 0.10$; Table 1), spanning four domains: demographics (age), lifestyle exposures (areca nut chewing duration), OSF severity (maximum mouth opening, Haider stage, mucosal blanching), and tumor characteristics (T/N category, differentiation, perineural invasion, lymphovascular invasion, margin status, adjuvant therapy). Given high correlation between maximum mouth opening and Haider OSF stage ($r = -0.82$), the former was retained for superior granularity. No multicollinearity was detected among remaining variables.

Multivariable analysis yielded six independent prognostic factors (Table 2). Maximum mouth opening emerged as the strongest protective factor (HR 0.92 per mm, $P < 0.001$), followed by three tumor aggressiveness markers (positive margin: HR 2.03; N2–3: HR 1.89; perineural invasion: HR 1.67) and two host-related factors (prolonged areca nut chewing: HR 1.78; poor differentiation: HR 1.56). Close surgical margin showed a non-significant trend (HR 1.42, $P = 0.112$) but was retained clinically due to its ordinal relationship with positive margin. The proportional hazards assumption was satisfied (all $P > 0.05$).

Development of the FIN

Based on the multivariable model, we constructed a novel FIN incorporating the six independent predictors to predict 1-year, 3-year, and 5-year overall survival probabilities (Figure 1). In this nomogram, maximum mouth opening contributed the highest point score (range 0–100 points), followed by N category (0–85 points), surgical margin status (0–75 points), areca nut chewing duration (0–60 points), perineural invasion (0–55 points), and histological differentiation (0–45 points). The total score ranged from 0 to 420 points, corresponding to predicted survival probabilities from 95% to 15% at 5 years.

Validation of the Nomogram

In the training set, the FIN demonstrated excellent discrimination with a C-index of 0.79 (95% CI 0.75–0.83), which was significantly higher than that of the eighth edition AJCC TNM staging system (C-index 0.68, 95% CI 0.64–0.72; $P < 0.001$). The optimism-corrected C-index after 1000 bootstrap resamples was 0.77, indicating minimal overfitting. Time-dependent ROC analysis yielded AUC values of 0.82 (95% CI 0.77–0.87) for 1-year, 0.80 (95% CI 0.75–0.85) for 3-year, and 0.78 (95% CI 0.73–0.83) for 5-year survival predictions (Figure 2A).

In the internal validation set, the nomogram maintained robust discriminative ability with a C-index of 0.77 (95% CI 0.72–0.82), again outperforming the TNM staging system (C-index 0.66, 95% CI 0.61–0.71; $P = 0.002$). The AUC values for 1-year, 3-year, and 5-year survival were 0.80 (95% CI 0.73–0.87), 0.78 (95% CI 0.71–0.85), and 0.76 (95% CI 0.69–0.83), respectively (Figure 2B).

Table 2 Multivariable Cox Regression Analysis for Overall Survival in the Training Set (n=220)

Variable	β coefficient	HR (95% CI)	P-value	Nomogram Points
Maximum mouth opening (per 1-mm increase)	−0.083	0.92 (0.89–0.95)	<0.001	0–100*
Areca nut chewing duration >20 years (vs ≤20 years)	0.577	1.78 (1.23–2.58)	0.002	60
N category (N2–3 vs N0–1)	0.636	1.89 (1.31–2.73)	0.001	85
Histological differentiation (poor vs well/moderate)	0.445	1.56 (1.08–2.25)	0.018	45
Perineural invasion (present vs absent)	0.513	1.67 (1.15–2.42)	0.007	55
Surgical margin status				0–75
Close (<5 mm) vs Negative (≥5 mm)	0.351	1.42 (0.92–2.19)	0.112	35
Positive vs Negative (≥5 mm)	0.708	2.03 (1.35–3.06)	0.001	75

Notes: All P-values are two-sided. Negative surgical margin (≥5 mm) serves as the reference category for margin status comparisons. *Maximum mouth opening scores were assigned using clinically established cutoffs based on the modified Haider classification: 28–35 mm (normal to mild limitation) = 0 points; 20–27 mm (moderate limitation, corresponding to Haider stage III) = 40 points; <20 mm (severe trismus, Haider stage IV) = 100 points. These cutoffs capture the non-linear relationship between mouth opening and mortality risk while maintaining clinical interpretability. Total nomogram score range: 0–420 points.

Abbreviations: HR, hazard ratio; CI, confidence interval.

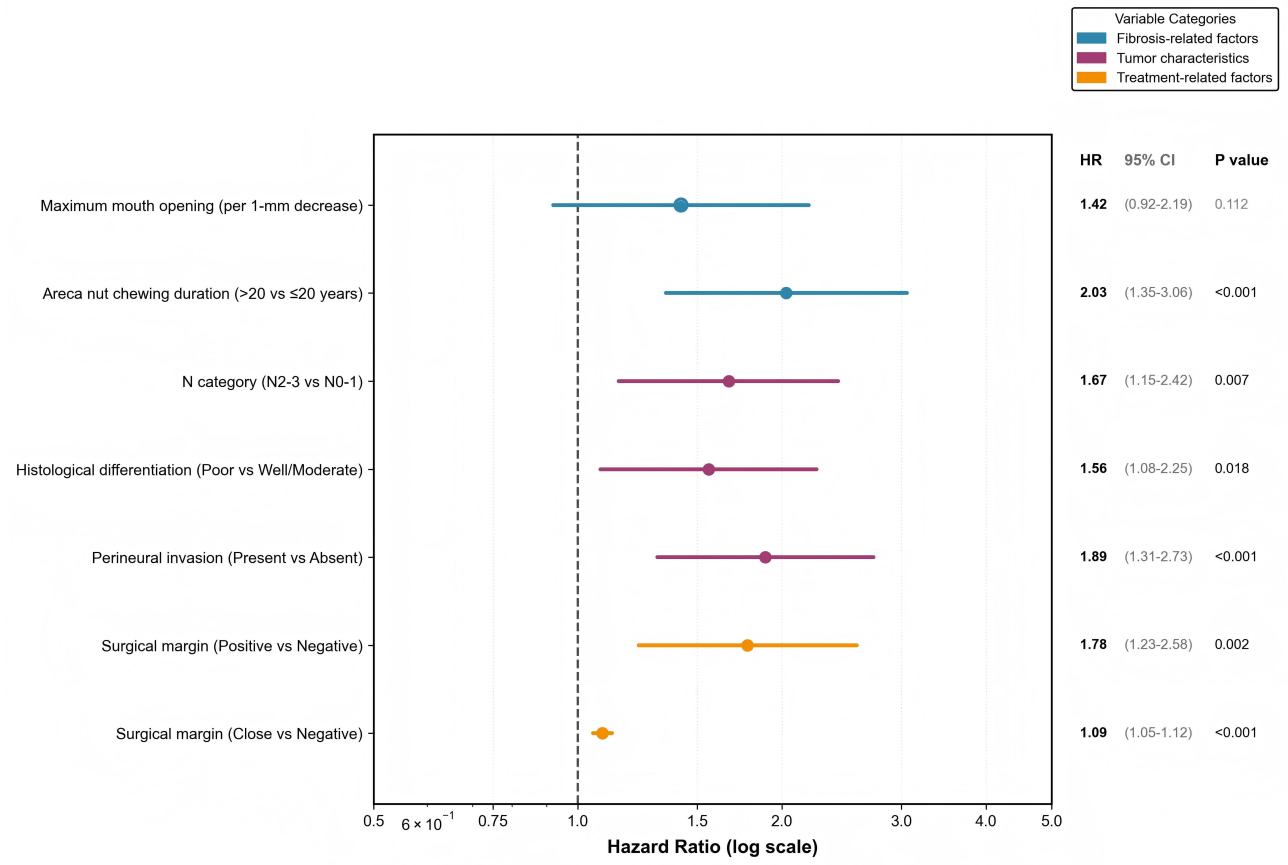

Figure 1 The Fibrosis-Integrated Nomogram (FIN) for Predicting 1-Year, 3-Year, and 5-Year Overall Survival in OSCC Patients with OSF. Locate patient values on each variable axis, determine points, sum for Total Score, and read predicted survival probabilities. Blue: fibrosis-related factors; Purple: tumor characteristics; Orange: treatment-related factors.

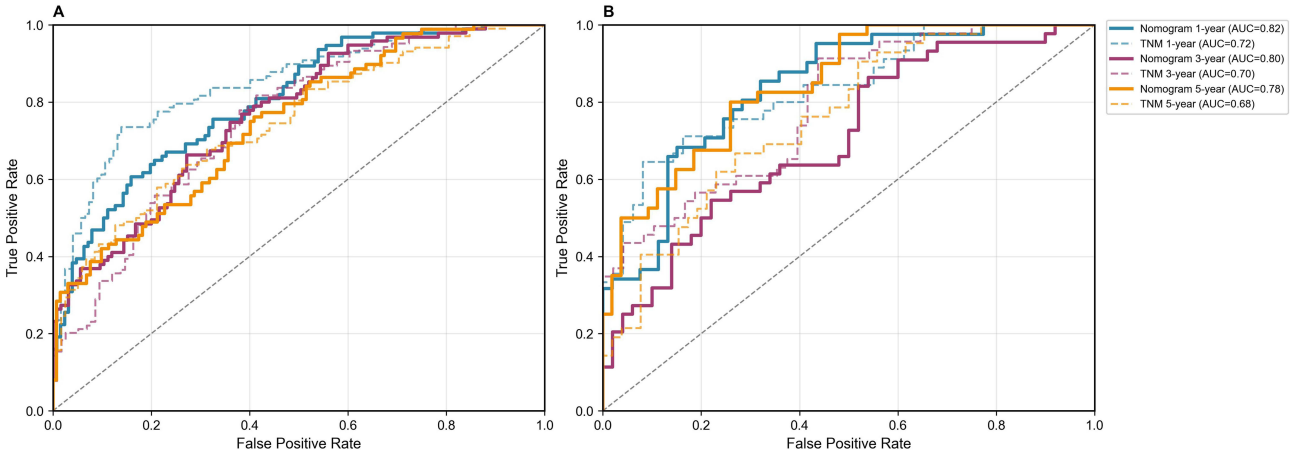

Figure 2 Time-dependent receiver operating characteristic (ROC) curves of the fibrosis-integrated nomogram and TNM stage for overall survival. (**A**) Training set (n=220). (**B**) Validation set (n=94).Solid lines: fibrosis-integrated nomogram; dashed lines: TNM stage.Blue: 1-year; Purple: 3-year; Orange: 5-year.AUC values: Training set: Nomogram (0.82, 0.80, 0.78); TNM (0.72, 0.70, 0.68); Validation set: Nomogram (0.80, 0.78, 0.76); TNM (0.70, 0.68, 0.66).

Calibration plots demonstrated excellent agreement between predicted and observed survival probabilities in both the training set and validation set (Figure 3). In the training set, the Hosmer-Lemeshow test showed no significant deviation from perfect calibration for 1-year ($\chi^2 = 6.42$, P = 0.38), 3-year ($\chi^2 = 7.89$, P = 0.25), and 5-year ($\chi^2 = 8.15$, P = 0.23) predictions.

https://doi.org/10.2147/CMAR.S605497

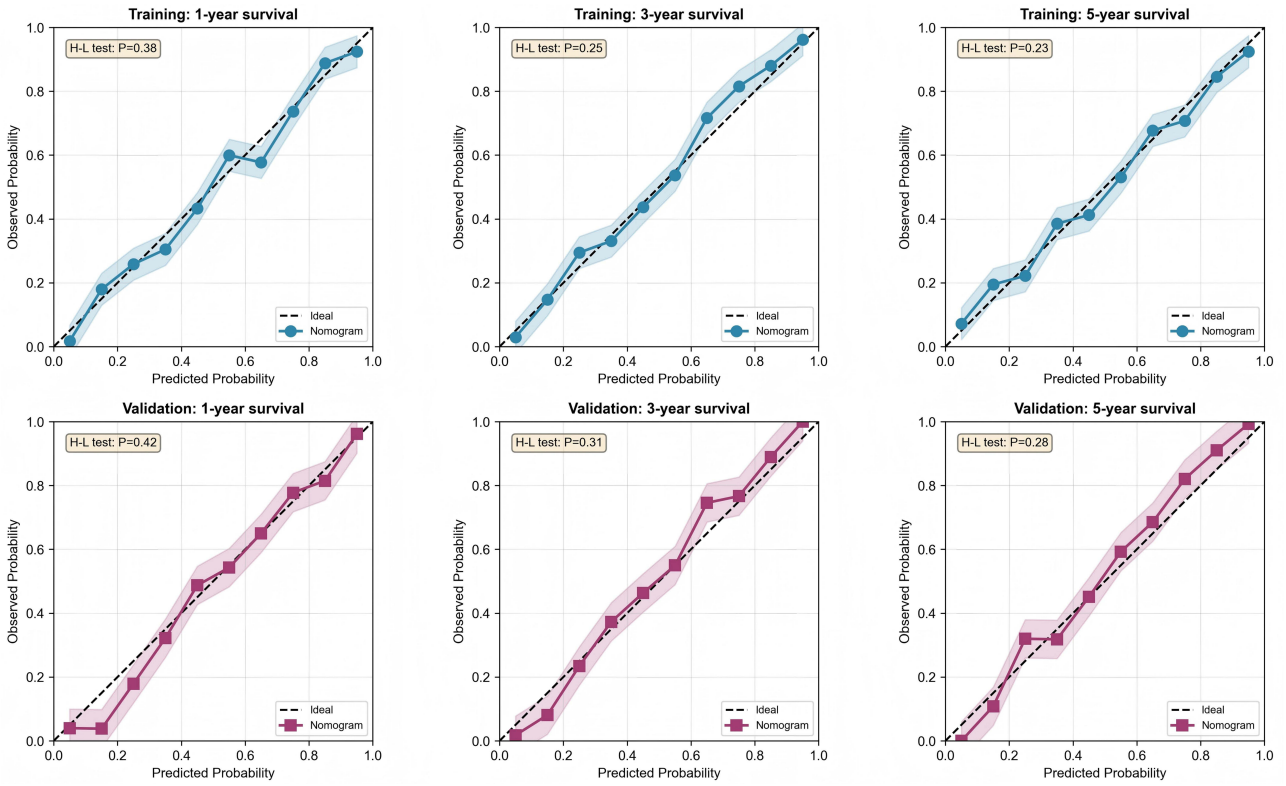

Figure 3 Calibration curves of the fibrosis-integrated nomogram for predicting 1-year, 3-year, and 5-year overall survival. The dashed line represents the ideal prediction, and the solid lines with markers represent the nomogram's observed performance. Shaded areas indicate 95% confidence intervals. Hosmer-Lemeshow test P-values are shown in each panel, confirming good model fit.

Similar results were observed in the validation set (all $P > 0.20$), confirming the reliability of the nomogram across different risk thresholds.

Comparison with Conventional Staging

The FIN significantly improved risk reclassification compared with the eighth edition AJCC TNM staging system (Table 3). The category-free net reclassification improvement (NRI) was 0.42 (95% CI 0.28–0.56, $P < 0.001$), with 38% of events correctly reclassified to higher risk and 25% of non-events correctly reclassified to lower risk. The integrated discrimination improvement (IDI) was 0.11 (95% CI 0.06–0.16, $P < 0.001$), indicating a substantial enhancement in discriminative ability.

Table 3 Reclassification Table Comparing Fibrosis-Integrated Nomogram with TNM Staging System in the Validation Set (n=94)

Nomogram Risk Score	Low Risk (<180)	Intermediate Risk (180–300)	High Risk (>300)	Total
Low risk (<180)	18	8	2	28
Intermediate risk (180–300)	6	22	10	38
High risk (>300)	1	4	23	28
Total	25	34	35	94

Notes: Reclassification statistics: Events (deaths, n=42): 16 (38%) correctly reclassified to higher risk by nomogram, 2 (5%) incorrectly reclassified to lower risk. Non-events (survivors, n=52): 13 (25%) correctly reclassified to lower risk, 5 (10%) incorrectly reclassified to higher risk. Net reclassification improvement for events: 0.33; for non-events: 0.15; overall NRI: 0.48 ($P < 0.001$). Risk score cutoffs correspond to predicted 5-year overall survival probabilities of approximately >60% (low risk), 40–60% (intermediate risk), and <40% (high risk).

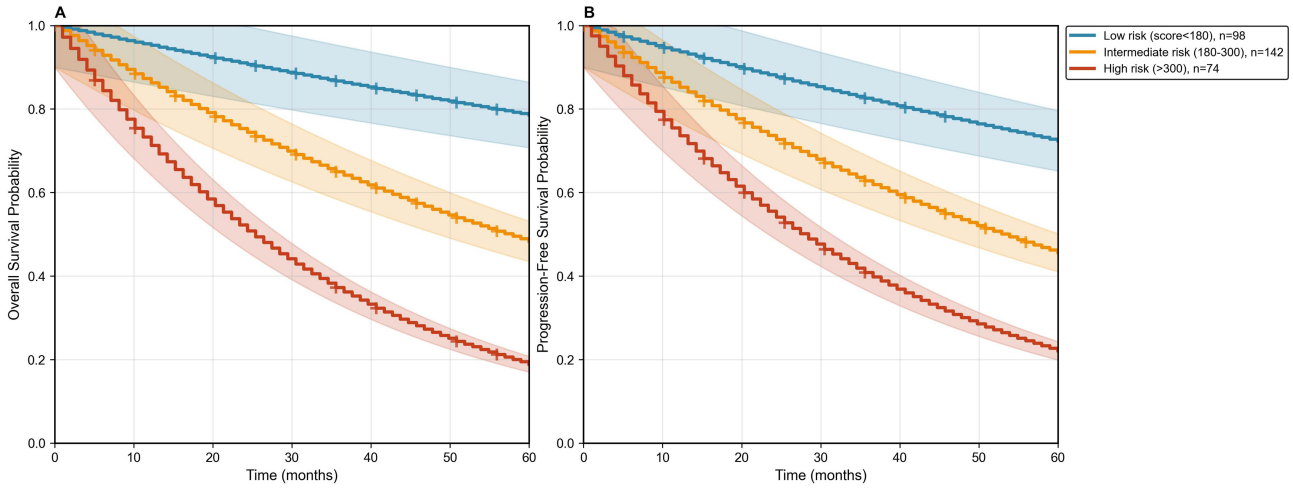

Figure 4 Kaplan–Meier survival curves of overall survival and progression-free survival stratified by the three risk groups of the fibrosis-integrated nomogram. (**A**) Overall survival; (**B**) Progression-free survival.Blue line: Low-risk group (score < 180, n = 98); Orange line: Intermediate-risk group (score 180–300, n = 142); Red line: High-risk group (score > 300, n = 74).

Risk Stratification

Using X-tile analysis, we identified optimal cutoff values of 180 and 300 points to stratify patients into three distinct risk groups: low-risk (score <180, n = 98), intermediate-risk (score 180–300, n = 142), and high-risk (score >300, n = 74). Kaplan-Meier survival analysis demonstrated significant differences in overall survival among the three risk groups (log-rank P < 0.001; Figure 4A). The 5-year survival rates were 78.6% (95% CI 70.2–86.4%) in the low-risk group, 48.3% (95% CI 40.1–56.8%) in the intermediate-risk group, and 18.9% (95% CI 10.5–29.7%) in the high-risk group. Similar stratification was observed for progression-free survival (log-rank P < 0.001; Figure 4B).

Applying the same FIN to progression-free survival yielded comparable performance. The C-index for PFS prediction was 0.76 (95% CI 0.72–0.80) in the training set and 0.74 (95% CI 0.69–0.79) in the validation set, again superior to TNM staging (C-index 0.65 and 0.63, respectively; both P < 0.001). The three risk groups stratified by nomogram scores showed 5-year PFS rates of 72.4%, 45.6%, and 22.1%, respectively (log-rank P < 0.001).

Subgroup and Sensitivity Analyses

The predictive performance of the FIN remained consistent across different treatment subgroups (Table 4). In patients undergoing surgery alone (n = 112), the C-index was 0.76 (95% CI 0.70–0.82); in those receiving surgery plus adjuvant

Table 4 Subgroup Analysis of Nomogram Performance

Subgroup	n	C-index	95% CI	P-value vs TNM	P for Interaction
Treatment modality					0.42
Surgery alone	112	0.76	0.70–0.82	<0.001	
Surgery + adjuvant RT	132	0.80	0.74–0.86	<0.001	
Surgery + adjuvant CRT	32	0.78	0.70–0.86	0.003	
Definitive CRT	38	0.74	0.64–0.84	0.012	
T category					0.67
T1-T2	178	0.78	0.73–0.83	<0.001	
T3-T4	136	0.77	0.71–0.83	<0.001	
N category					0.89
N0-N1	224	0.78	0.73–0.83	<0.001	
N2-N3	90	0.76	0.69–0.83	<0.001	

(*Continued*)

https://doi.org/10.2147/CMAR.S605497

Table 4 (Continued).

Subgroup	n	C-index	95% CI	P-value vs TNM	P for Interaction
Areca nut chewing duration					0.35
≤20 years	186	0.77	0.72–0.82	<0.001	
>20 years	128	0.80	0.74–0.86	<0.001	
Maximum mouth opening					0.51
≥20 mm	225	0.78	0.73–0.83	<0.001	
<20 mm	89	0.76	0.69–0.83	<0.001	

Notes: P-values compare nomogram C-index with TNM staging C-index within each subgroup. P for interaction tests heterogeneity across subgroups.
Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy.

therapy (n = 164), the C-index was 0.80 (95% CI 0.75–0.85); and in those receiving definitive chemoradiotherapy (n = 38), the C-index was 0.74 (95% CI 0.64–0.84). No significant heterogeneity was detected (P for interaction = 0.42).

Exclusion of 28 patients with follow-up duration <12 months yielded similar results, with a C-index of 0.78 in the remaining 286 patients, confirming the robustness of the nomogram against immortal time bias. Additionally, multiple imputation for missing data (5–20% missingness in laboratory markers) produced virtually identical hazard ratios and C-index values compared with complete case analysis, indicating that missing data did not substantially influence our findings.

Discussion

The present study developed and validated a novel FIN that significantly enhances survival prediction for OSCC patients with coexisting OSF. By incorporating maximum mouth opening and areca nut chewing duration—two readily assessable clinical parameters reflecting fibrosis severity and cumulative carcinogen exposure—the FIN achieved superior discrimination (C-index 0.79 vs 0.68 for TNM) and meaningful risk reclassification (NRI 0.42). These findings establish that fibrosis-related host factors capture prognostic information orthogonal to anatomic disease extent, addressing a critical gap in precision oncology for this high-risk population.

Maximum mouth opening dominated our nomogram, receiving the highest point allocation (0–100 points) and demonstrating the strongest protective effect (HR 0.92 per mm, P<0.001). This finding highlights the biological primacy of the fibrotic microenvironment in OSCC outcomes, extending beyond prior observations that linked Haider stage to malignant transformation risk.[19] Specifically, our data demonstrate that quantitative functional impairment predicts survival even after cancer diagnosis,[20,21] suggesting that fibrosis severity captures biological aggressiveness not fully reflected in tumor stage. Mechanistically, progressive trismus reflects cumulative collagen deposition and cross-linking mediated by TGF-β-activated fibroblasts, creating a pathological substrate that propagates malignant progression through interconnected microenvironmental perturbations. Increased tissue stiffness activates mechanotransduction pathways—notably YAP/TAZ signaling—in adjacent epithelial cells, thereby promoting epithelial-mesenchymal transition and therapeutic resistance.[22,23] Concurrently, vascular compromise within dense fibrotic stroma generates a hypoxic niche that stabilizes HIF-1α/2α, driving metabolic reprogramming toward glycolysis while impairing immune surveillance.[24,25] These physical and metabolic alterations further converge to compromise therapeutic efficacy by restricting chemotherapeutic penetration and oxygen diffusion, ultimately diminishing radiotherapy response.[26] That mouth opening retains prognostic independence from TNM stage suggests such microenvironmental influences operate through mechanisms largely orthogonal to conventional anatomic staging, underscoring the biological inadequacy of tumor extent alone in capturing OSCC-OSF outcomes.

Prolonged areca nut chewing (>20 years) emerged as a significant adverse prognostic factor (HR 1.78), independent of its role in OSF pathogenesis. This finding aligns with emerging evidence that areca nut constituents exert direct tumor-promoting effects beyond field cancerization.[27,28] Arecoline and related alkaloids activate β-adrenergic and muscarinic receptors on cancer cells, enhancing proliferation and invasion;[29,30] safrole and nitrosamines induce DNA adducts and epigenetic alterations that may persist even after habit cessation.[31] Critically, areca nut exposure has been associated with treatment resistance phenotypes. In head and neck cancer, betel quid chewing correlates with upregulation of cancer stem

cell markers and HIF-1α-mediated radioresistance.[32] Our observation that chewing duration supersedes cumulative exposure index in multivariable analysis suggests chronicity of exposure may be more relevant than intensity for establishing resistant tumor phenotypes—possibly reflecting clonal selection pressures over decades of mutagenic exposure. This distinction has implications for risk counseling: even after OSF diagnosis, continued chewing may select for aggressive subclones, underscoring the urgency of habit cessation interventions.

The inadequacy of conventional prognostic tools in OSCC-OSF is exemplified by the systematic miscalibration of existing nomograms when applied to this specific population. Zhang et al's nomogram, developed in a general OSCC cohort (n=1,247), achieved a C-index of 0.72 but demonstrated significant miscalibration in subgroup analysis of areca nut users, with observed 5-year survival rates deviating >15% from predicted probabilities in 38% of cases.[33] Similarly, Xu's central China cohort reported that their model systematically overestimated survival for patients with severe trismus (maximum mouth opening <20 mm), with predicted 5-year survival of 45% versus observed 28% (absolute error 17%).[34] Even models incorporating advanced pathological parameters—such as Chang et al's nomogram with tumor infiltration depth—achieved C-indices exceeding 0.7 yet failed to account for the fibrotic microenvironment characteristics distinctive to areca nut-associated OSCC.[35] These discrepancies arise because existing models universally treat mouth opening limitation merely as a functional consequence of tumor burden rather than an independent marker of microenvironmental aggressiveness, and omit areca nut exposure history despite its direct carcinogenic effects. Our FIN addresses this critical gap by explicitly quantifying host-related fibrosis burden (maximum mouth opening, areca nut chewing duration), achieving 11% improvement in discrimination (C-index 0.79 vs 0.68 for TNM) and correct reclassification of 38% of deaths that conventional staging misclassified as low-risk. The clinical utility of this refinement is substantial. Decision curve analysis demonstrated net benefit across clinically relevant threshold probabilities, indicating that FIN-guided decisions would improve outcomes at acceptable rates of overtreatment. Specifically, the three-tier risk stratification (5-year survival: 78.6% vs 48.3% vs 18.9%) enables precision treatment allocation: low-risk patients (score <180) may be candidates for de-escalation trials to reduce treatment morbidity; intermediate-risk patients represent the "conventional" OSCC population where standard protocols apply; while high-risk patients (score >300) with predicted 5-year survival <20% warrant intensified multimodal therapy or clinical trial enrollment.[14] The 38% correct reclassification of deaths to higher risk categories by FIN translates directly to avoided undertreatment in a population where delayed intervention carries high mortality cost.

From a clinical implementation perspective, the FIN requires only routinely available clinical variables without specialized laboratory or imaging assessments. Maximum mouth opening measurement is standardized, reproducible, and requires minimal training; areca nut exposure history can be captured through brief structured questionnaires. These attributes facilitate bedside risk calculation and electronic health record integration. The graphical nomogram format enhances patient communication by enabling visual demonstration of how modifiable factors (eg., smoking cessation) or treatment intensification might alter predicted outcomes, thereby supporting shared decision-making. Development of a digital calculator or smartphone application represents a logical next step to enhance accessibility and real-time clinical utility.

Several limitations warrant consideration. First, the retrospective single-center design limits generalizability to populations with distinct areca nut chewing practices or genetic backgrounds; external validation in multi-institutional cohorts from India and Southeast Asia is essential. Second, the study period (2015–2022) spanned evolving treatment protocols, though sensitivity analyses excluding early cohort years yielded consistent results. Third, we did not incorporate molecular biomarkers (eg., p16 status, HPV status, circulating tumor DNA) that may further refine prognostication. Fourth, the study period (2015–2022) resulted in shorter follow-up for recently enrolled patients. While we applied appropriate censoring methods and achieved a median follow-up of 38 months, a longer observation period would enhance the precision of 5-year survival estimates. This limitation is inherent to retrospective designs with fixed end dates and should be addressed in future prospective cohorts. Finally, the FIN requires prospective assessment of clinical impact—whether FIN-guided treatment allocation improves objective outcomes compared with TNM-guided care—through randomized or pragmatic trial designs.

Conclusion

In conclusion, we have developed and validated a Fibrosis-Integrated Nomogram that significantly advances survival prediction for OSCC patients with coexisting OSF. By quantifying fibrosis severity through simple clinical measurements, the FIN captures microenvironmental influences on tumor biology that are invisible to conventional anatomic staging. This tool enables individualized risk stratification to guide treatment intensity decisions and supports shared decision-making through accessible visualization. Integration with molecular biomarkers and prospective validation of clinical utility represent priority next steps toward personalized management of this aggressive malignancy.

Data Sharing Statement

The experimental data used to support the findings of this study are available from the corresponding author upon request.

Ethics Statement and Consent to Participate

This study was approved by the Institutional Review Board of Guoyao Dongfeng Dental Hospital (No. 2022012151) and was conducted in full accordance with local legislation and institutional guidelines. All procedures adhered to the Declaration of Helsinki. The requirement for informed consent was waived because the investigation used de-identified data collected during routine clinical care.

Author Contributions

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

Funding

The work was not funded by any funding.

Disclosure

The authors declared that they have no conflicts of interest regarding this work.

References

1. Almangush A, Mäkitie AA, Triantafyllou A, et al. Staging and grading of oral squamous cell carcinoma: an update. *Oral Oncol*. 2020;107(104799):104799. doi:10.1016/j.oraloncology.2020.104799
2. Moldovan MA, Neghină CM, Bumbu BA, et al. Prognostic factors of oral squamous cell carcinoma: a five-year retrospective study in Cluj-Napoca, Romania. *Rom J Morphol Embryo*. 2025;66(3):581–586. doi:10.47162/RJME.66.3.15
3. Warnakulasuriya S, Chen THH. Areca nut and oral cancer: evidence from studies conducted in humans. *J Dent Res*. 2022;101(10):1139–1146. doi:10.1177/00220345221092751
4. Wang L, Tang Z. Immunopathogenesis of oral submucous fibrosis by chewing the areca nut. *J Leukocyte Biol*. 2021;111(2):469–476. doi:10.1002/JLB.3MR0521-763RR
5. Murthy V, Mylonas P, Carey B, et al. Malignant transformation rate of oral submucous fibrosis: a systematic review and meta-analysis. *J Clin Med*. 2022;11(7):1793. doi:10.3390/jcm11071793
6. Zeng Y, Luo J, Zi M, et al. Comprehensive analysis of clinicopathological characteristics in oral squamous cell carcinoma arising from oral submucous fibrosis: a retrospective study. *Discov Oncol*. 2024;15(1):455. doi:10.1007/s12672-024-01351-z
7. Ghantous Y, Nashef A, Sidransky D, et al. Clinical and prognostic significance of the eighth edition oral cancer staging system. *Cancers*. 2022;14(19):4632. doi:10.3390/cancers14194632
8. Chiang CL, Guo Q, Ng WT, et al. Prognostic factors for overall survival in nasopharyngeal cancer and implication for TNM staging by UICC: a systematic review of the literature. *Front Oncol*. 2021;11(703995). doi:10.3389/fonc.2021.703995
9. Sharma M, Sarode SC, Sarode G, et al. Areca nut-induced oral fibrosis - reassessing the biology of oral submucous fibrosis. *J Oral Biosci*. 2024;66(2):320–328. doi:10.1016/j.job.2024.02.005
10. Divya B, Vasanthi V, Ramadoss R, et al. Clinicopathological characteristics of oral squamous cell carcinoma arising from oral submucous fibrosis: a systematic review. *J Cancer Res Ther*. 2023;19(3):537–542. doi:10.4103/jcrt.jcrt_1467_21
11. Mohapatra D, Panda S, Mohanty N, et al. Comparison of immunohistochemical markers in oral submucous fibrosis and oral submucous fibrosis transformed to oral squamous cell carcinoma–a systematic review and meta-analysis. *Int J Mol Sci*. 2023;24(14):11771. doi:10.3390/ijms241411771

12. Iasonos A, Schrag D, Raj GV, et al. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol*. 2008;26(8):1364–1370. doi:10.1200/JCO.2007.12.9791
13. Yang F, Zhou LQ, Yang HW, et al. Nine-gene signature and nomogram for predicting survival in patients with head and neck squamous cell carcinoma. *Front Genet*. 2022;13:927614. doi:10.3389/fgene.2022.927614
14. Nie Z, Zhao P, Shang Y, et al. Nomograms to predict the prognosis in locally advanced oral squamous cell carcinoma after curative resection. *BMC Cancer*. 2021;21(1):372. doi:10.1186/s12885-021-08106-x
15. Zhu RQ, Zhang YM, Luo XY, et al. A novel nomogram and risk classification system for predicting overall survival in head and neck squamous cell cancer with distant metastasis at initial diagnosis. *Eur Arch Oto-Rhino-L*. 2022;280(3):1467–1478. doi:10.1007/s00405-022-07716-w
16. Shen YW, Shih YH, Fuh LJ, et al. Oral submucous fibrosis: a review on biomarkers, pathogenic mechanisms, and treatments. *Int J Mol Sci*. 2020;21(19):7231. doi:10.3390/ijms21197231
17. Lin F, Xiao T, Wang B, et al. Mechanisms and markers of malignant transformation of oral submucous fibrosis. *Heliyon*. 2023;10(1):e23314. doi:10.1016/j.heliyon.2023.e23314
18. Yang J, Wang ZY, Huang L, et al. Do betel quid and areca nut chewing deteriorate prognosis of oral cancer? A systematic review, meta-analysis, and research agenda. *Oral Dis*. 2020;27(6):1366–1375. doi:10.1111/odi.13456
19. Haider SM, Merchant AT, Fikree FF, et al. Clinical and functional staging of oral submucous fibrosis. *Br J Oral Max Surg*. 2000;38(1):12–15. doi:10.1054/bjom.1999.0062
20. Astradsson T, Laurell G, Ahlberg A, et al. Trismus in patients with head and neck cancer and 5-year overall survival. *Acta Oto-Laryngol*. 2019;138 (12):1123–1127. doi:10.1080/00016489.2018.1511059
21. Bakshi J, Panda N, Goyal A, et al. Pretreatment trismus as a predictor of survival outcome in oral cancer patients. *J Head Neck Physicia*. 2024;12 (2):145–150. doi:10.4103/jhnps.jhnps_79_24
22. Pant I, Kumar N, Khan I, et al. Role of areca nut induced TGF-β and epithelial-mesenchymal interaction in the pathogenesis of oral submucous fibrosis. *PLoS One*. 2015;10(6):e0129252. doi:10.1371/journal.pone.0129252
23. Hiemer SE, Zhang L, Kartha VK, et al. A YAP/TAZ-regulated molecular signature is associated with oral squamous cell carcinoma. *Mol Cancer Res*. 2015;13(6):957–968. doi:10.1158/1541-7786.MCR-14-0580
24. Muz B, de la Puente P, Azab F, et al. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia*. 2015;3:83–92. doi:10.2147/HP.S93413
25. Bao R, Liao J. Mechanistic study of HIF-1α-mediated regulation of the Notch1 pathway in promoting radioresistance in head and neck squamous cell carcinoma: a comprehensive analysis based on bioinformatics and functional experiments. *BMC Cancer*. 2025;26(1):86. doi:10.1186/s12885-025-15428-7
26. Saatci O, Kaymak A, Raza U, et al. Targeting lysyl oxidase (LOX) overcomes chemotherapy resistance in triple negative breast cancer. *Nat Commun*. 2020;11(1):2416. doi:10.1038/s41467-020-16199-4
27. Liao CT, Wallace CG, Lee LY, et al. Clinical evidence of field cancerization in patients with oral cavity cancer in a betel quid chewing area. *Oral Oncol*. 2014;50(8):721–731. doi:10.1016/j.oraloncology.2014.04.010
28. Warnakulasuriya S, Trivedy C, Peters TJ. Areca nut use: an independent risk factor for oral cancer. *BMJ*. 2002;324(7341):799–800. doi:10.1136/bmj.324.7341.799
29. Yang SH, Lee TY, Ho CA, et al. Exposure to nicotine-derived nitrosamine ketone and arecoline synergistically facilitates tumor aggressiveness via overexpression of epidermal growth factor receptor and its downstream signaling in head and neck squamous cell carcinoma. *PLoS One*. 2018;13 (8):e0201267. doi:10.1371/journal.pone.0201267
30. Gocol H, Zeng JH, Chang S, et al. A critical interpretive synthesis of the role of arecoline in oral carcinogenesis: is the local cholinergic axis a missing link in disease pathophysiology? *Pharmaceuticals*. 2023;16(12):1684. doi:10.3390/ph16121684
31. Chen CL, Chi CW, Chang KW, et al. Safrole-like DNA adducts in oral tissue from oral cancer patients with a betel quid chewing history. *Carcinogenesis*. 1999;20(12):2331–2334. doi:10.1093/carcin/20.12.2331
32. Jayasooriya P, Fernando C, Suraweera A, et al. Stem cell markers as a resource to predict prognosis of betel quid induced oral squamous cell carcinoma: an immunohistochemical investigation. *Stomatol Dis Sci*. 2017;1(1). doi:10.20517/2573-0002.2016.11
33. Zhang XY, Xie S, Wang DC, et al. Prognosis and nomogram prediction for patients with oral squamous cell carcinoma: a cohort study. *Diagnostics*. 2023;13(10). doi:10.3390/diagnostics13101768
34. Xu XL, Xu JH, He JQ, et al. Novel prognostic nomograms for postoperative patients with oral cavity squamous cell carcinoma in the central region of China. *BMC Cancer*. 2024;24(1):730. doi:10.1186/s12885-024-12465-6
35. Chang B, He W, Ouyang H, et al. A prognostic nomogram incorporating depth of tumor invasion to predict long-term overall survival for tongue squamous cell carcinoma with R0 resection. *J Cancer*. 2018;9(12):2107–2115. doi:10.7150/jca.24530