Nomograms to Predict the Prognosis in Locally Advanced Oral Squamous Cell Carcinoma After Curative Resection

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Abstract

Background: Oral squamous cell carcinoma (OSCC), the dominant histologic type of oral cancer. Locally advanced OSCC remains a major therapeutic challenge. Our study aimed to develop and validate nomograms predicting survival prognosis in patients with locally advanced oral squamous cell carcinoma (OSCC) after curative resection.

Methods: A total of 269 consecutive patients with primary OSCC who received curative resection between September 2007 and March 2020 were retrospectively enrolled in our study. Patients were randomly assigned to the training cohort (n=201) or the validation cohort (n=68). Multivariate Cox regression analyses were conducted to determine independent prognostic factors for overall survival (OS) and cancer specific survival (CSS) in the training set, which were used for the construction of nomogram models estimating 3-, and 5-year OS and CSS. We also evaluated the nomograms using concordance indices (c-index), calibration curves, and decision curve analyses (DCA), and compared those with the AJCC 8th staging system. The results were externally validated in the validation cohort.

Results: Age, Kaplan-Feinstein (KFI) index, pT, the number of positive nodes and systemic inflammatory index (SII) were significant prognostic predictors for OS and CSS. The OS nomogram had c-index values of 0.712 in the training set and 0.697 in the validation set, while the CSS nomograms had c-index values of 0.709 in the training set and 0.675 in the validation set. These data were superior to those of AJCC 8th staging system, suggesting high discriminative ability of the nomograms. Calibration curves exhibited good agreement between observed and predicted survival. DCA curves indicated the nomograms were with potential clinical usefulness. These results were validated in the validation set.

Conclusions: The novel nomograms incorporating clinically available characteristics for OS and CSS prediction were developed in the locally advanced OSCC patients after curative surgery. Validation revealed good discrimination and calibration, indicating the clinical utility of the nomograms in the individualized prognosis prediction of locally advanced OSCC after curative surgery.

Background

Oral cavity cancer is one of the most common malignancies worldwide, with an estimated incidence of 355,000 new cases per year[1]. Oral squamous cell carcinoma (OSCC), the dominant histologic type of oral cancer, accounts for 95% of oral tumors[2]. The overall age standardized incidence rate is 21 per 100,000 in male and 17 per 100,000 in female[3]. Despite the spreading of multimodal treatment approaches, the prognosis of OSCC, especially locally advanced OSCC, have not improved significantly for the past 30 years[4-6]. Locally advanced OSCC remains a major therapeutic challenge. A better understanding of the prognostic factors is necessary for appropriate risk stratification of patients, optimization of therapeutic approaches and individualization of patient care.

The staging of OSCC based on American Joint Committee on Cancer (AJCC) TNM system has been used for several years to estimate OSCC patients' survival in clinical practice[7]. However, the traditional TNM staging system is often inadequate as the prognosis of OSCC varies on a number of factors that are related to not only the tumor size, distant metastasis and nodal status, but also to the other clinical pathological features such as tumor site, tumor grade, nodal involvement, and presence of lymphovascular invasion, as well as to the patient specific characteristics such as age, smoking and comorbidities[8]. Hence, the consideration of prognostic relevant clinical-pathologic factors could offer accurate prognostic information.

Various reports have shed light on the probable prognostic significance of certain biomarkers in the setting of OSCC, of which serum biomarkers are of potential clinical utility due to their feasibility and accessibility. Multiple serum biomarkers including lymphocyte count, neutrophil-lymphocyte ratio (NLR), and platelet–lymphocyte ratio (PLR) have been proposed and validated as significant prognosticators in a broad spectrum of cancer[9-12]. Recently, the systemic immune-inflammation index (SII) combining neutrophil, lymphocyte and platelet, has been reported to provide prognostic information in several malignancies. Diao P et al.[13] found that preoperative SII could serve as a powerful prognostic predictor in patients with primary OSCC.

Prognostic models integrating a set of clinical attributes offer greater precision in clinical outcome prediction. Nomograms are statistical tools to visualize complex models that use a set of clinical characteristics for prediction of individual patient outcome[14]. Nowadays, nomograms have been widely used as a user-friendly tool for evaluating the prognosis of various cancers[15-17]. What's more, the recurrence and staging of prostate cancers via nomograms have been included into the NCCN clinical guidelines[18]. However, nomograms for predicting the prognosis of locally advanced OSCC is scarce.

The present study was a retrospective analysis of a cohort of patients with locally advanced OSCC in an academic tertiary care center. The aim of our study was to determine the prognostic significance of different clinical-pathologic factors, and establish the first nomograms using the most relevant prognostic factors to estimate the probabilities of OS, and cancer specific survival (CSS) in patients with locally advanced OSCC for better risk stratification and clinical decision-making.

Methods

Study Subjects

From September 2007 to March 2020, a total of 269 consecutive patients with primary OSCC diagnosed at a university hospital were retrospectively recruited. All patients were histopathologically confirmed of locally advanced (stage III or IV non-metastatic) OSCC. Patients who had early tumor (stage I or II), recurrent or metastasized cancer, other concomitant primary cancer, prior history of malignancy, preoperative chemotherapy, radiotherapy or contradictions of surgery were excluded. All enrolled patients underwent primary tumor resection per our institutional guidelines. Following the surgery, the pathological

TNM classification was established using the AJCC 8th edition. Postoperative chemotherapy and/or radiotherapy were performed selectively based on our institutional guidelines.

Two thirds of these patients were randomly assigned to the training set (n=201) to establish the predictive models and the remaining patients (n=68) were assigned to the validation set to evaluate the performance of the models.

Data collection

Patients' data were collected from electronic records including age at diagnosis, gender, comorbidity, smoking status, preoperative blood tests, TNM stage, tumor grade, presence of perineural invasion, depth of tumor invasion, number of positive nodes, lymphovascular invasion, primary tumor site, extracapsular extension, bone invasion, and safety margins. All identifiable information stored was strictly followed per the hospital's guidance. Cigarette smokers were defined as individuals who reported having smoked more than 100 cigarettes during their lifer time and/or smoked every day for at least 1 year. The pathological TNM classification of all tumors was established per the AJCC Staging Manual (2010). Patient comorbidity was assessed by using the Kaplan-Feinstein index (KFI)[19].

The whole blood samples for neutrophil, monocyte and platelet counts were harvested within 3 days before surgery. Systematic immune-inflammation index (SII), was calculated from preoperative counts of peripheral blood platelets (P), neutrophils (N) and lymphocytes (L) to the following equation: SII = P x N/L. NLR and PLR were defined as follows: NLR=N/L, PLR=P/L. SPSS software was used to employ the cut-off values of SII, NLR and PLR for OS. The results revealed that the optimal cut-off values were of 535.5 for SII, 2.8 for NLR and 162.5 for PLR.

After discharge, patients were followed-up every 3 month for the first three years, every 6 month until 5 years and annually thereafter. OS was defined as the time interval from the date of surgery to the end of the study or death. Cancer specific survival (CSS) was defined as the time elapsed between the date of surgery and the death attributed to OSCC, or the end of the study.

All the procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study has been approved by the ethics committee of The Second Hospital of Dalian Medical University. Informed consent was obtained from all patients.

Statistical Analysis

Continuous variables were compared by Student's t test or Mann-Whitney U test, while categorical variables were compared by Chi-square test or Fisher's exact test. OS and CSS were estimated by Kaplan-Meier method and the statistical differences in survival compared by log-rank tests. COX proportional hazards regression models were used to identify the independent prognostic predictors for OS and CSS. Subsequently, these significant predictors in the training set were used to establish nomogram models in

R software. The concordance index (C-index) was calculated to quantify the predictive accuracy of the nomograms. Calibration plots were generated to check the consistency between the predicted and observed probabilities[20]. In the external validation, the total points of each patient were generated based on the established nomograms. Thereafter, the Cox regression analyses were carried out by using the patients' total points as a factor. Additionally, C-index and calibration curves were derived in the validation set. Decision curve analysis was employed to examine the clinical net benefit of a predictive model by using rmda package in R software[21]. Finally, we compared the performance of the nomograms with AJCC 8th edition TNM staging system by using the c-index and decision curve analysis methods.

All statistical analyses were analyzed using SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA) and R software version 3.5.2 (http://www.r-project.org) with R packages cmprsk, rmda, rms, and survival packages. A two-tailed P value <0.05 was considered statistically significant.

Results

Clinicopathological Characteristics of the study cohort

A total of 269 OSCC patients (204 male and 65 female), with a median age of 62 years (range, 21-85 years) were enrolled in this study. The tumors were most frequently located on the mobile tongue and floor of the mouth. 67.9% of the patients were well or moderately differentiated. Cervical lymph node dissection was performed in 266 patients. Regarding the treatment, 113 patients received radiotherapy exclusively after surgery, 100 patients underwent concomitant radiotherapy and chemotherapy after surgery, and 51 patients just had surgical resection without adjuvant radiotherapy. **Table 1** presented patient demographic and tumor variables of the study cohort. In total, 201 patients were assigned into the training set, while 68 patients were assigned into the validation set. The two groups exhibited similar demographic and tumor parameters (P<0.05).

Survival Analyses

The median follow-up period was 55 months (ranging from 2-95 months). At the end of follow-up, a total of 115 patients died, with 74 patients dying of cancer-related causes and 41 patients dying of other causes.

In the training set, the OS rates at 3- and 5-year were 66.4% (95%CI: 63.5%-69.3%) and 55.6% (95%CI: 49.5%-61.7%), respectively, while the CSS rates at 3- and 5-year were 78.3% and 66.2% respectively. In the validation set, the OS rates at 3- and 5-year were 63.0% and 55.4%, respectively, while the CSS rates at 3- and 5-year were 70.2% and 61.6%, respectively.

Overall Survival

The results of the univariate and multivariate models for overall survival are provided in **Table 2**. Age, KFI index, pT, pN, AJCC stage, the number of positive nodes, NLR, PLR and SII were significant predictors of

overall survival in the univariate analysis. On multivariate analysis, age (P<0.001), KFI index (P=0.003), pT (P<0.001), the number of positive nodes (P=0.009) and SII (P<0.001) remained to be significant prognosticators.

CSS

On univariate analysis, age, KFI index, pT, pN, AJCC stage, the number of positive nodes, safety margins, SII, NLR and PLR had a statistically significant impact on CSS. The results of multivariate model demonstrated the following variables as potential independent risk factors of CSS: age (P<0.001), KFI index (P=0.003), pT (P=0.003), the number of positive nodes (P=0.008) and SII (P<0.001) (**Table 3**).

Nomograms construction

Based on the results of COX regression analyses, we constructed prognostic nomograms for 3-year and 5-year OS and CSS (**Figure 1**). The point of each factor can be determined by drawing the vertical line from the variable to the point axis. By summing up the total score and locating it on the total point scale, we can get the estimated survival probability at each time point.

Nomogram validation

Nomogram validation was assessed using the c-index values and calibration curves. The c-index values showed that the established nomograms had good discriminative abilities with 0.712 for OS and 0.709 for CSS. **Figure 2** showed the calibration plots for the nomogram models of OS and CSS in the training set in which nomograms predicated 3-year and 5- year OS and CSS probabilities were well matched with the actual probabilities.

When subjected to the external validation, the nomograms also discriminated to a good extent with c index values of 0.697 for OS and 0.675 for CSS. Calibration plots (**Figure 3**) indicated the good consistency between nomograms predicted and actual probabilities in validation set, which suggested the good accuracy of the established nomograms.

Survival analyses according to the risk stratification based on the nomograms

The total points of each patient were generated from the established nomograms. All the patients were evenly divided into three subgroups per the total points. With regards for OS, the three groups were low risk group (≤145), medium risk group (145-190), and high risk group (>190). For CSS, the three groups were low risk group (≤102), medium risk group (102-141), and high risk group (>141). As shown in **Figure 4**, patients in the high risk group had distinctly lower OS and CSS survival probabilities (P < 0.001).

Comparison of the nomogram with the AJCC staging

Compared to the AJCC staging system, our nomograms had statistically higher c-indices for OS and CSS prediction in locally advanced OSCC patients, which were summarized in **Table 4**. Decision curve analysis (DCA) has been proposed as a method to assess the clinical validity of the prediction models. The DCA

plots demonstrated the established nomogram models were associated with improved clinical net benefits over the AJCC stages with wider ranges of threshold probabilities in both training (**Figure 5**) and validation sets (**Figure 6**).

Discussion

Nomograms enable visualize the prognostic strength of various relevant factors in a single model which allow them to have more accurate survival prediction than conventional TNM staging system or an individual molecular biomarker. Nomograms have been widespread used in the prognosis prediction in clinical oncology. Compared with the other cancers, nomograms have been sparingly studied for head and neck tumors. For OSCC, several studies have reported on the development of nomograms to predict the survival[22-25]. However, to our knowledge, there was no study specifically for the locally advanced OSCC patients. The present study was the first attempt to investigate the usage of nomograms for survival prediction of locally advanced OSCC.

Our nomograms were constructed based on the COX proportional hazards regression analyses in the training set of 201 locally advanced OSCC patients after curative surgery. In the multivariate analyses, we found that advanced age, KFI, pT, the number of positive nodes and SII were significant prognosticators for OS and CSS. Based on these significant prognosticators, we developed the nomograms for OS and CSS. The nomograms showed good discrimination abilities with C-index values of 0.712 for OS and 0.709 for CSS. Calibration curves demonstrated satisfactory agreement between the nomograms and actual survival. Moreover, the nomograms exhibited the net clinical benefit using DCA. We also externally validated the nomograms performance in a validation set of 68 patients. External validation also supported the satisfactory accuracy and calibration of our nomograms. Besides, the performance of nomograms was, in turn, validated by Kaplan-Meier curves which showed distinct prognosis in three subgroups sorting by the total points of the nomograms.

The significant prognosticators incorporated in our nomograms were clinically feasible and economical, especially including the novel preoperative systemic inflammation-immune biomarker SII. Notably, accumulating evidence demonstrated that inflammatory cells including neutrophils, platelets, monocytes and lymphocytes carry out a robust role in contributing to proliferation and survival of malignant cells, angiogenesis and metastasis[26]. Many reports also have revealed the significant prognostic values of preoperative systemic inflammation-immune biomarkers, for example, NLR, PLR and LMR, in various types of cancers[9-12]. Recently, SII based on neutrophils, lymphocytes and platelets, has been demonstrated as a novel integrated biomarker and exhibited prognostic value in several tumors including advanced pancreatic cancer[27], cervical cancer[28], gastric cancer[29] and colorectal cancer[30]. The study published in 2018[13] reported for the first time that high preoperative SII was associated with poor outcome and could be served as an independent prognostic predictor in patients with OSCC. Elevated SII probably resulted from neutrophilia, thrombocythemia and lymphopenia. Solid tumor-related neutrophilia, after excluding obvious reasons such as infections, bone marrow metastasis and the usage of

corticosteroid, may arise from hematopoietic colony-stimulating factors and inflammatory cytokines triggered by tumors including granulocyte colony-stimulating factor and others[31 32]. Neutrophils could facilitate tumor growth by the secretion of various chemokines and cytokines, as well as actively recruiting other tumor-supporting cells to the tumor microenvironment[33]. What's more, tumor associated neutrophils play the critical role in the metastasis process by inhibiting the activity of natural killer cells and enhancing the extravasation of tumor cells, mainly through secreting various matrix metalloproteinases to degrade and modify the extracellular matrix[34]. Thrombocythemia usually promote tumor progression and metastasis. Several studies showed that cancer incidence could increase in patients with abnormally elevated platelet count and those with over 3.5×10^{11}/L count probably have more than a 3% risk of cancer in one year of observation[35 36]. A meta-analysis suggested platelet quantity as a potential prognostic marker in pancreatic cancer[37]. Tumors firstly activate platelets through tissue factors -containing microparticles (MPs). The platelet MPs can express signals and communicate with a variety of cells to induce angiogenesis[38 39]. Also platelets or platelet activation can directly interact with cancer cells, synergistically promotes TGF-β and NF-kB pathways in cancer which in turn triggers the epithelial mesenchymal transition of cancer cells to facilitate tumor metastasis[36]. Lymphopenia has been frequently observed in patients with advanced cancers and shown as a powerful prognostic factor in advanced solid tumors including renal cell carcinoma, colorectal, lung cancer and breast cancer[40-43]. Lymphocytes as major immune cells play a fundamental role in cell-mediated immunologic destruction of cancer cells, although different subtypes of lymphocytes vary in their functional roles against cancer [44 45]. Thus, lymphopenia could be considered as indicative of impaired immune surveillance and contribute to the favorable tumor microenvironment for tumor metastasis. In our study, multivariate analyses revealed that SII was a powerful prognosticator of OS and CSS in advanced OSCC.

Concerning clinical-pathologic factors, the most important prognosticators were age, comorbidity, depth of invasion (DOI), extranodal extension (ENE), number of positive nodes, perineural invasion (PNI) and tumor grade. Advanced age and greater comorbidity have been reported by various studies on the upper aerodigestive tract tumors, as elderly patients or patients in poor general health are more vulnerable to disease progression and not eligible for invasive therapies. Consistent with previous findings, our data also confirmed advanced age and greater comorbidity as the independently clinical prognostic factors in advanced OSCC patients. Tumor grade wasn't identified as a prognostic factor in our data, which probably can be explained by the homogeneity of the study population in terms of patients and tumor profiles.

DOI has been advocated to be associated with tumor metastasis and worse survival outcomes, and included in the AJCC 8^{th} T staging classification. In our study, pT classification was independently associated with worse prognosis. Lymph nodal involvement has been a well-established prognostic factor in head and neck cancers. The AJCC 8^{th} staging has included lymph nodal site (ipsilateral and contralateral), size, presence of ENE in the nodal staging category. The negative impact of ENE has been fully incorporated in the AJCC 8^{th} N staging system, where it leads to upstaging nodal positive OSCC,

whatever size, number, or laterality of the positive node(s)[7]. However, the number of lymph node is probably overestimated in the system, as just greater than one lymph node is staging as N2, without considering the increasing number of positive lymph nodes as further stratification. Several clinical studies have observed the prognostic significance of number of positive lymph nodes in OSCC, albeit with different cut-off values[46]. Roberts et al. [47] reported that the number of positive lymph nodes model (0, 1, 2-4 and ≥5) performed better than AJCC 7th edition N staging model in head and neck cancers. Moreover, a recent publication by Rajappa et al.[48] revealed that the number of positive lymph nodes (0, 1, 2, >2) could outperform AJCC 8th nodal staging system in the prediction of OS and DFS in oral cancer. Subramaniam et al.[49] categorized the number of positive lymph nodes as 0, 1-2, 3-4 and ≥5 and exhibited it was superior to LNR and LODSS in the prediction of OS and DFS in 643 OSCC patients. In our study, we adopted the categorization system proposed by Subramaniam et al[49]. We also observed the inverse relationship between the number of positive lymph nodes and patients' survival, and confirmed its prognostic significance for OS and CSS in advanced OSCC patients.

Based on the independent prognosticators discussed above, we built the first nomograms predicting OS and CSS in locally advanced OSCC patients and internal and external validations showed our models with relatively high c-indices and well-fitted calibration curves. AJCC 8th staging system is currently used system for assessment of prognosis in locally advanced OSCC patients. We performed comparative analysis between our developed nomograms and AJCC staging system. Our nomograms outperformed the AJCC 8th staging system for OS and CSS prediction in locally advanced OSCC patients, with statistically higher c-indices. Additionally, in the DCA analyses, the nomograms exhibited to be more beneficial over AJCC 8th staging system in the prognosis prediction of OS and CSS. These data demonstrated that our nomograms had better performance with clinical utility in prognosis prediction.

The present study had two main limitations. Firstly, our study was a retrospective study so that the selection bias was inevitable. Secondly, the patients enrolled were from a single institution, which may not represent the entire locally advanced OSCC patients. Notwithstanding these limitations, our study built the first nomograms predicting OS and CSS in locally advanced OSCC patients. More importantly, robust internal and external validation demonstrated sufficient discriminatory power and accurate calibration in our proposed nomograms. Additionally, the main advantages of the present study were that all the included prognosticators were feasible and accessible in daily clinical practice.

Conclusions

In conclusion, we constructed and validated nomograms based on clinically available characteristics for predicting 3- and 5- year OS and CSS in patients with locally advanced OSCC. The novel nomograms displayed relatively good performance with potential clinical utility, which would aid the individualized risk stratifying the patients and contribute to the individualized disease management.

Abbreviations

AJCC: American Joint Committee on Cancer; CSS: cancer specific survival; DOI: depth of invasion; ENE: extranodal extension; HR: hazard ratio; NLR: neutrophil-lymphocyte ratio; OSCC: Oral squamous cell carcinoma; OS: overall survival; PLR: and platelet–lymphocyte ratio; PNI: perineural invasion; SII: systemic immune-inflammation index.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of The Second Hospital of Dalian Medical University. Informed consent was obtained from all patients.

Consent for publication

Not appliable.

Availability of data and materials

The data used in the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors disclose no conflicts of interest.

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Author’s contributions

ZL N, PC Z, and B S conceived of and designed the study. ZL N, PC Z, and B S generated the figures and tables. YS S and B S analyzed the data. B S wrote the manuscript and ZL N and PC Z critically reviewed the manuscript. All authors have read and approved the manuscript.

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Tables

Table 1 Clinicopathological Characteristics of the study cohort

Characteristics	Training cohort(n=201)	Validation cohort(n=68)	P Value
Gender			0.639
Female	50(24.9)	15(22.1)	
Male	151(75.1)	53(77.9)	
Age	62.7±11.6	62.8±11.9	0.956
KFI			0.257
<2	125(62.19)	37(54.41)	
≥2	76(37.81)	31(45.59)	
Smoking			0.679
No	121(60.2)	39(57.35)	
Yes	80(39.8)	29(42.65)	
pT			0.359
T1	41(20.4)	12(17.65)	
T2	63(31.34)	21(30.88)	
T3	54(26.87)	15(22.06)	
T4	43(21.39)	20(29.41)	
pN			0.259
N0	31(15.42)	9(13.24)	
N1	53(26.37)	14(20.59)	
N2	110(54.73)	40(58.82)	
N3	7(3.48)	5(7.35)	
AJCC Stage			0.544
III	61(30.3)	18(26.5)	
IV	140(69.7)	50(73.5)	
Perineural invasion			0.931
No	120(59.7)	41(60.3)	
Yes	81(40.3)	27(39.7)	
Tumor differentiation			0.640
Well differentiated	87(43.3)	25(36.8)	

Moderately differentiated	51(25.4)	19(27.9)	
Poorly differentiated	63(31.3)	24(35.3)	
Depth of tumor invasion			0.268
<20 mm	127(63.2)	48(70.6)	
≥20 mm	74(36.8)	20(29.4)	
Number of Positive Nodes			0.648
0	84(41.79)	31(45.6)	
1-2	58(28.86)	21(30.9)	
3-4	34(16.92)	9(13.2)	
≥5	25(12.44)	7(10.3)	
Lymphovascular invasion (%)			0.189
No	41(20.4)	9(13.24)	
Yes	160(79.6)	59(86.76)	
Primary Tumor Site			0.570
Tongue	69(34.33)	21(30.88)	
Floor of mouth	60(29.85)	25(36.76)	
Other	72(35.82)	22(32.35)	
Extracapsular extension			0.537
No	158(78.61)	51(75)	
Yes	43(21.39)	17(25)	
Bone invasion			0.366
No	119(59.2)	36(52.94)	
Yes	82(40.8)	32(47.06)	
Safety Margins			0.408
<5mm	45(22.39)	12(17.65)	
≥5mm	156(77.61)	56(82.35)	
SII			0.580
<535.5	120(59.7)	38(55.88)	
≥535.5	81(40.3)	30(44.12)	

NLR			0.480
<2.8	125(62.19)	39(57.35)	
≥2.8	76(37.81)	29(42.65)	
PLR			0.761
<162.5	114(56.72)	40(58.82)	
≥162.5	87(43.28)	28(41.18)	

Abbreviations: AJCC, American Joint Committee on Cancer; KFI, Kaplan-Feinstein index; NLR, neutrophil-lymphocyte ratio; PLR, platelet–lymphocyte ratio; SII, systematic immune-inflammation index.

Table 2 Univariate and multivariate analyses of OS in locally advanced OSCC patients

Characteristics	Univariate analysis	*P* Value	Multivariate analysis	*P* Value
	HR(95%CI)		HR(95%CI)	
Gender				
Female	Ref			
Male	1.034(0.908-1.179)	0.612		
Age	1.024(1.014-1.035)	**<0.001**	1.023(1.012-1.033)	**<0.001**
KFI				
<2	Ref		Ref	
≥2	1.389(1.087-1.776)	**0.009**	1.458(1.137-1.871)	**0.003**
Smoking				
No	Ref			
Yes	1.284(0.904-1.824)	0.163		
pT		**<0.001**		**<0.001**
T1	Ref		Ref	
T2	2.317(1.424-3.771)	0.001	2.128(1.303-3.477)	0.003
T3	2.869(1.79-4.598)	0	3.157(1.945-5.124)	0
T4	4.317(2.728-6.831)	0	4.316(2.674-6.966)	0
pN		**.073**		.065
N0	Ref		Ref	
N1	0.641(0.445-0.924)	0.017	1.031(0.701-1.517)	0.876
N2	0.825(0.618-1.101)	0.192	1.358(0.99-1.864)	0.058
N3	1.078(0.656-1.773)	0.766	1.685(1.01-2.811)	0.046
AJCC Stage				
III	Ref		Ref	
IV	1.526(1.863-1.251)	**<0.001**	1.358(0.99-1.864)	0.058
Perineural invasion				
No	Ref			
Yes	1.428(0.778-2.618)	0.250		
Tumor differentation		0.224		

Well differentiated	Ref			
Moderately differentiated	1.385(0.856-2.241)	0.184		
Poorly differentiated	2.581(0.452-14.724)	0.286		
Depth of tumor invasion				
<20 mm	Ref			
≥20 mm	1.385(0.856-2.241)	0.184		
Number of Positive Nodes		**0.002**		0.009
0	Ref		Ref	
1-2	1.483(1.112-1.979)	0.007	1.357(1.013-1.819)	0.041
3-4	1.725(1.238-2.402)	0.001	1.549(1.106-2.171)	0.011
≥5	1.782(1.203-2.64)	0.004	1.786(1.202-2.653)	0.004
Lymphovascular invasion (%)				
No	Ref			
Yes	2.581(0.452-14.724)	0.286		
Primary Tumor Site		0.245		
Tongue	Ref			
Floor of mouth	2.625(0.726-9.486)	0.141		
Other	1.306(0.939-1.817)	0.113		
Extracapsular extension				
No	Ref			
Yes	2.377(0.583-9.689)	0.227		
Bone invasion				
No	Ref			
Yes	1.244(0.887-1.743)	0.206		
Safety Margins				
<5mm	Ref			
≥5mm	1.397(0.766-2.547)	0.276		
SII				
<535.5	Ref		Ref	

≥535.5	1.724(1.354-2.194)	<0.001	1.599(1.25-2.047)	<0.001
NLR				
<2.8	Ref		Ref	
≥2.8	1.774(1.09-2.885)	0.021	2.243(0.751-6.704)	0.148
PLR				
<162.5	Ref		Ref	
≥162.5	2.472(1.127-5.424)	0.024	1.204(0.854-1.699)	0.289

Abbreviations: AJCC, American Joint Committee on Cancer; KFI, Kaplan-Feinstein index; NLR, neutrophil-lymphocyte ratio; PLR, platelet–lymphocyte ratio; SII, systematic immune-inflammation index.

Table 3 Univariate and multivariate analyses of CSS in locally advanced OSCC patients

Characteristics	Univariate analysis		Multivariate analysis	
	SHR(95%CI)	*P* Value	SHR(95%CI)	*P* Value
Age	1.372(1.221-1.541)	**0**	1.05(1.029-1.071)	**0**
Gender				
Female	Ref			
Male	1.034(0.908-1.179)	0.612		
KFI				
<2	Ref		Ref	
≥2	1.389(1.087-1.776)	**0.009**	1.706(1.109-2.624)	0.015
Smoking				
No	Ref			
Yes	1.284(0.904-1.824)	0.163		
pT		**0**		**0.004**
T1	Ref		Ref	
T2	2.317(1.424-3.771)	**0.001**	3.122(1.252-7.782)	**0.015**
T3	2.869(1.79-4.598)	**0**	5.073(2.077-12.392)	**0**
T4	4.317(2.728-6.831)	**0**	4.428(1.762-11.129)	**0.002**
pN		**0.073**		.625
N0	Ref		Ref	
N1	0.641(0.445-0.924)	0.017	0.871(0.451-1.68)	0.68
N2	0.825(0.618-1.101)	0.192	1.127(0.648-1.96)	0.671
N3	1.078(0.656-1.773)	0.766	1.575(0.626-3.965)	0.335
AJCC Stage				
III	Ref		Ref	
IV	1.728(1.413-2.113)	**0**	0.750(0.513-1.095)	0.136
Perineural invasion				
No	Ref			
Yes	1.225(0.844-1.777)	0.285		
Tumor differentation		0.235		

Well differentiated	Ref			
Moderately differentiated	1.774(0.627-5.016)	0.28		
Poorly differentiated	2.252(0.61-8.315)	0.223		
Depth of tumor invasion				
<20 mm	Ref			
≥20 mm	2.298(0.537-9.834)	0.262		
Number of Positive Nodes		**.009**		0.009
0	Ref		Ref	
1-2	1.564(1.076-2.272)	0.019	1.432(1.003-2.044)	0.048
3-4	2.079(1.307-3.308)	0.002	1.679(1.097-2.569)	0.017
≥5	2.487(1.572-3.935)	0.0001	2.413(1.349-4.318)	0.003
Lymphovascular invasion (%)				
No	Ref			
Yes	2.672(0.639-11.172)	0.178		
Primary Tumor Site				
Tongue	Ref			
Floor of mouth	1.815(0.593-5.55)	0.296		
Other	1.865(0.775-4.483)	0.164		
Extracapsular extension				
No	Ref			
Yes	1.866(0.775-4.494)	0.164		
Bone invasion				
No	Ref			
Yes	1.689(0.789-3.614)	0.177		
Safety Margins				
<5mm	Ref			
≥5mm	1.699(0.772-3.74)	0.188		
SII				
<535.5	Ref		Ref	

≥535.5	2.732(1.149-6.498)	0.023	2.214(1.289-3.805)	0.004
NLR				
<2.8	Ref		Ref	
≥2.8	1.164(1.022-1.326)	**0.022**	1.502(0.729-3.096)	0.27
PLR				
<162.5	Ref		Ref	
≥162.5	1.861(1.048-3.304)	**0.034**	2.246(0.732-6.885)	0.157

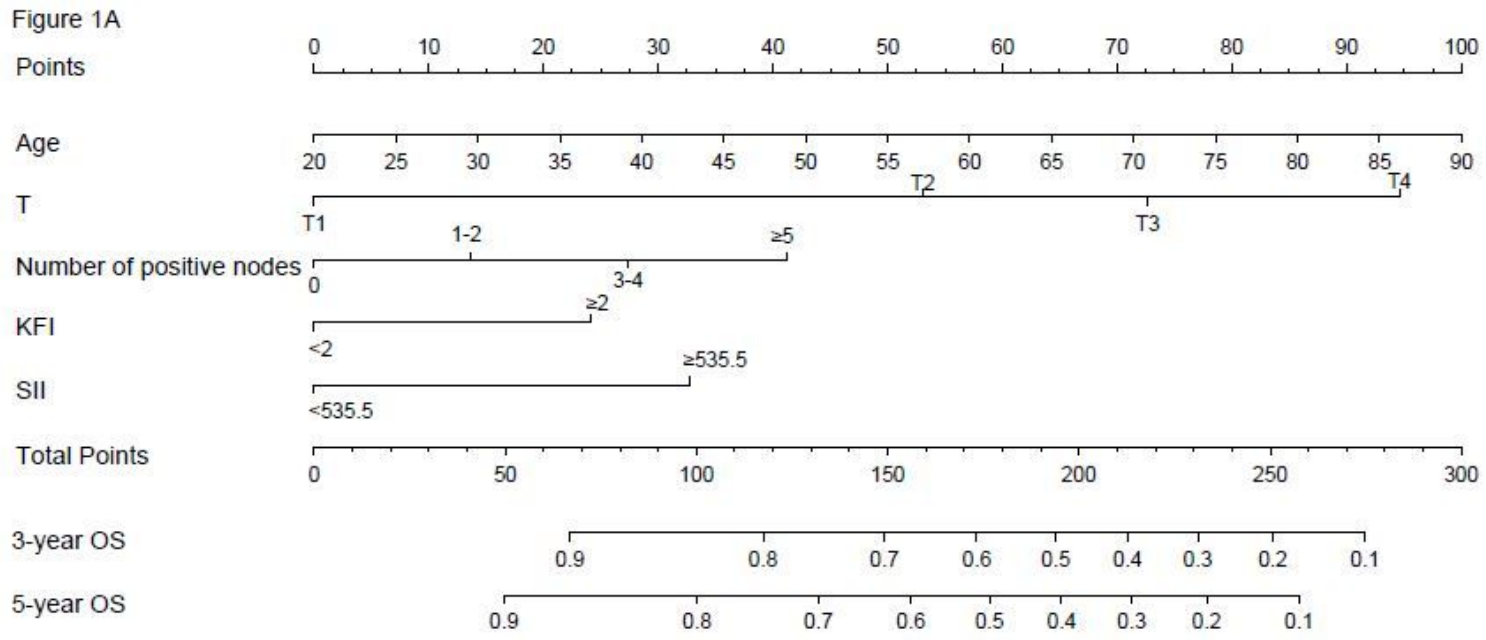
Abbreviations: AJCC, American Joint Committee on Cancer; KFI, Kaplan-Feinstein index; NLR, neutrophil-lymphocyte ratio; PLR, platelet–lymphocyte ratio; SII, systematic immune-inflammation index.

Table 4 Comparison of the nomograms with the AJCC staging

	Nomogram score	8th AJCC stage
Training Cohort		
OS	0.712(0.683-0.741)	0.567(0.563-0.571)
CSS	0.709(0.691-0.727)	0.611(0.593-0.629)
Validation Cohort		
OS	0.697(0.664-0.73)	0.582(0.549-0.615)
CSS	0.675(0.651-0.699)	0.598(0.574-0.622)

Abbreviations: AJCC, American Joint Committee on Cancer; CSS, cancer specific survival; OS, overall survival.

Figures



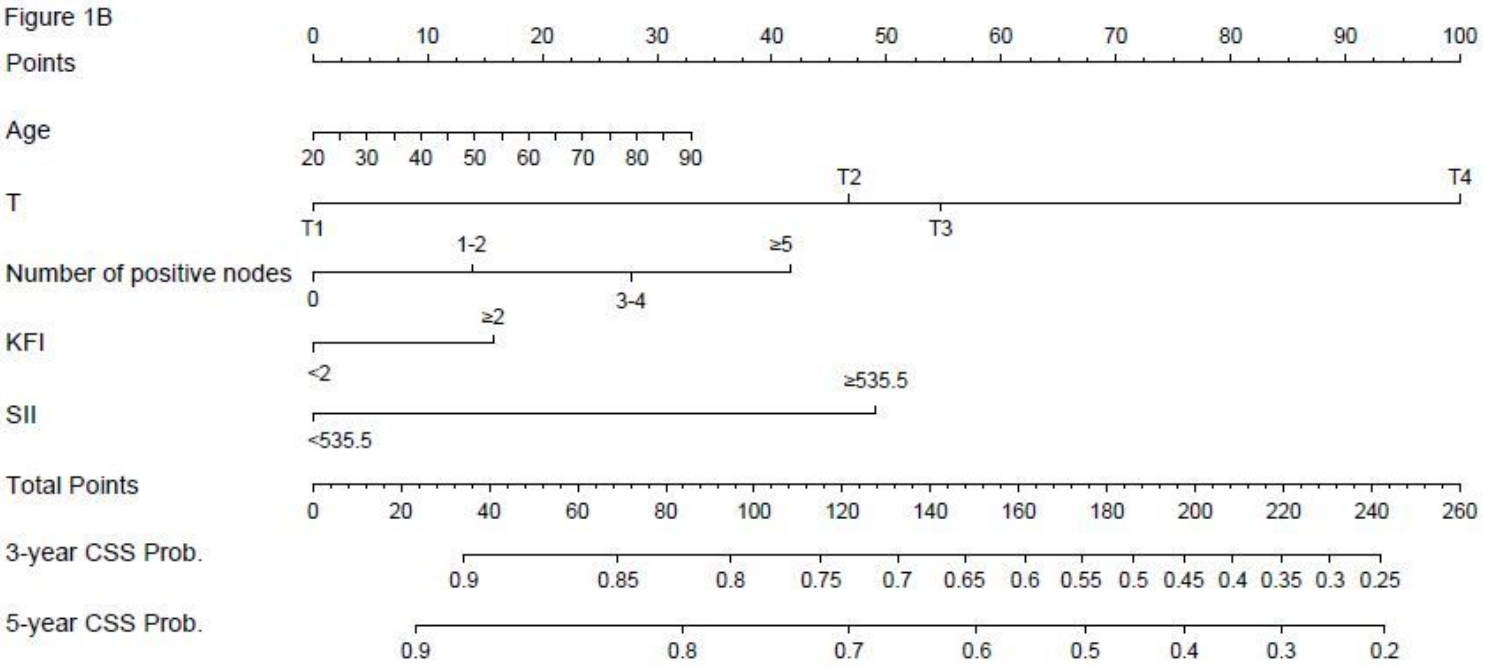


Figure 1

Nomograms for prognosis prediction in locally advanced OSCC patients. (A) 3-, and 5-year OS; (B) 3-, and 5-year CSS. Draw a straight line up to the point axis to determine the points assigned for each covariate. Sum the points and locate the total points on the bottom scale to determine the possibilities of 3- and 5-year OS and CSS in locally advanced OSCC patients. The higher total points indicate the lower expected survival. OS, overall survival; CSS, cancer specific survival.

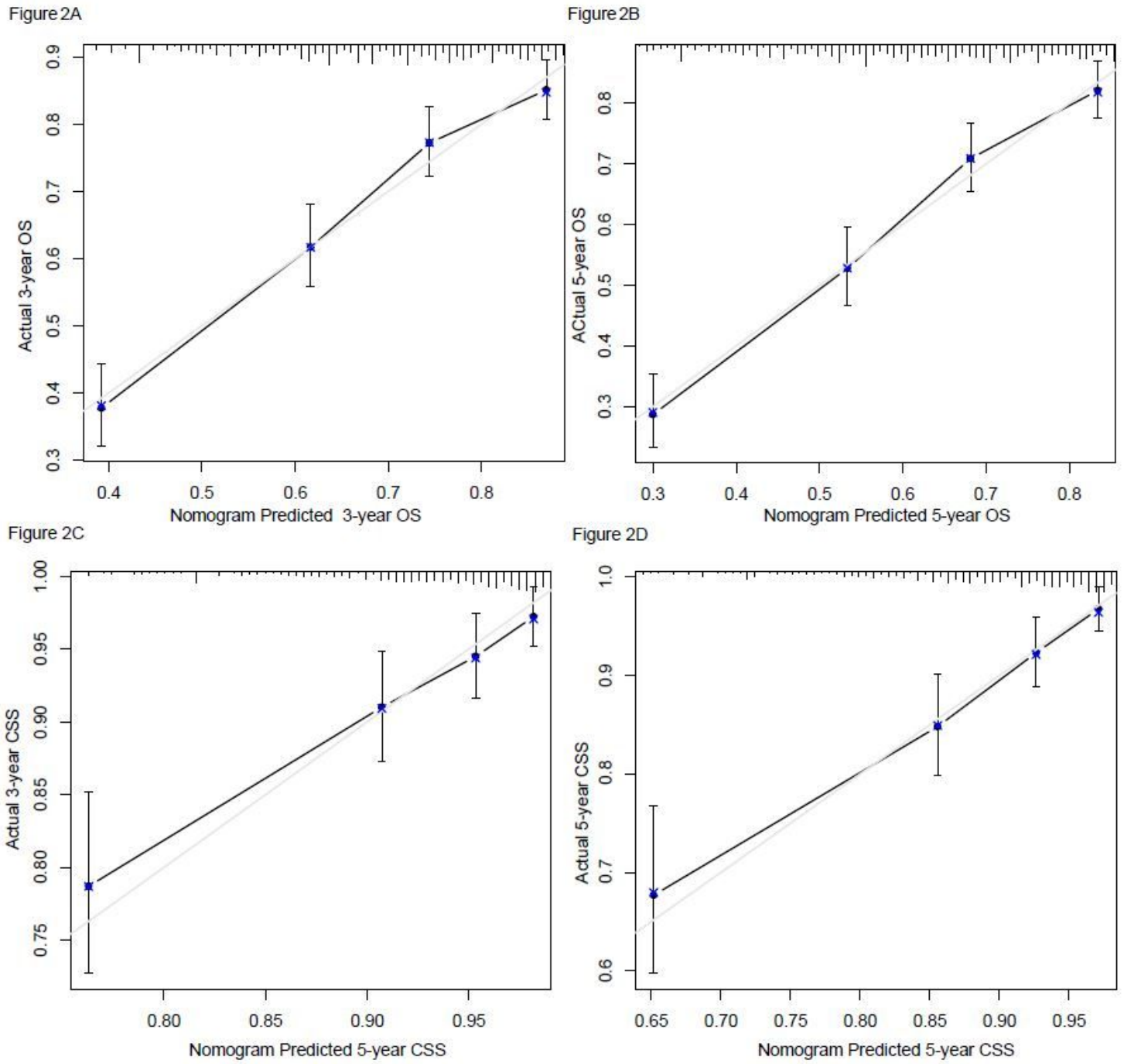


Figure 2

Calibration curves of nomograms in locally advanced OSCC patients in the validation cohort. (A) 3-year OS; (B) 5-year OS; (C) 3-year CSS; (D)5-year CSS. OS, overall survival; CSS, cancer specific survival.

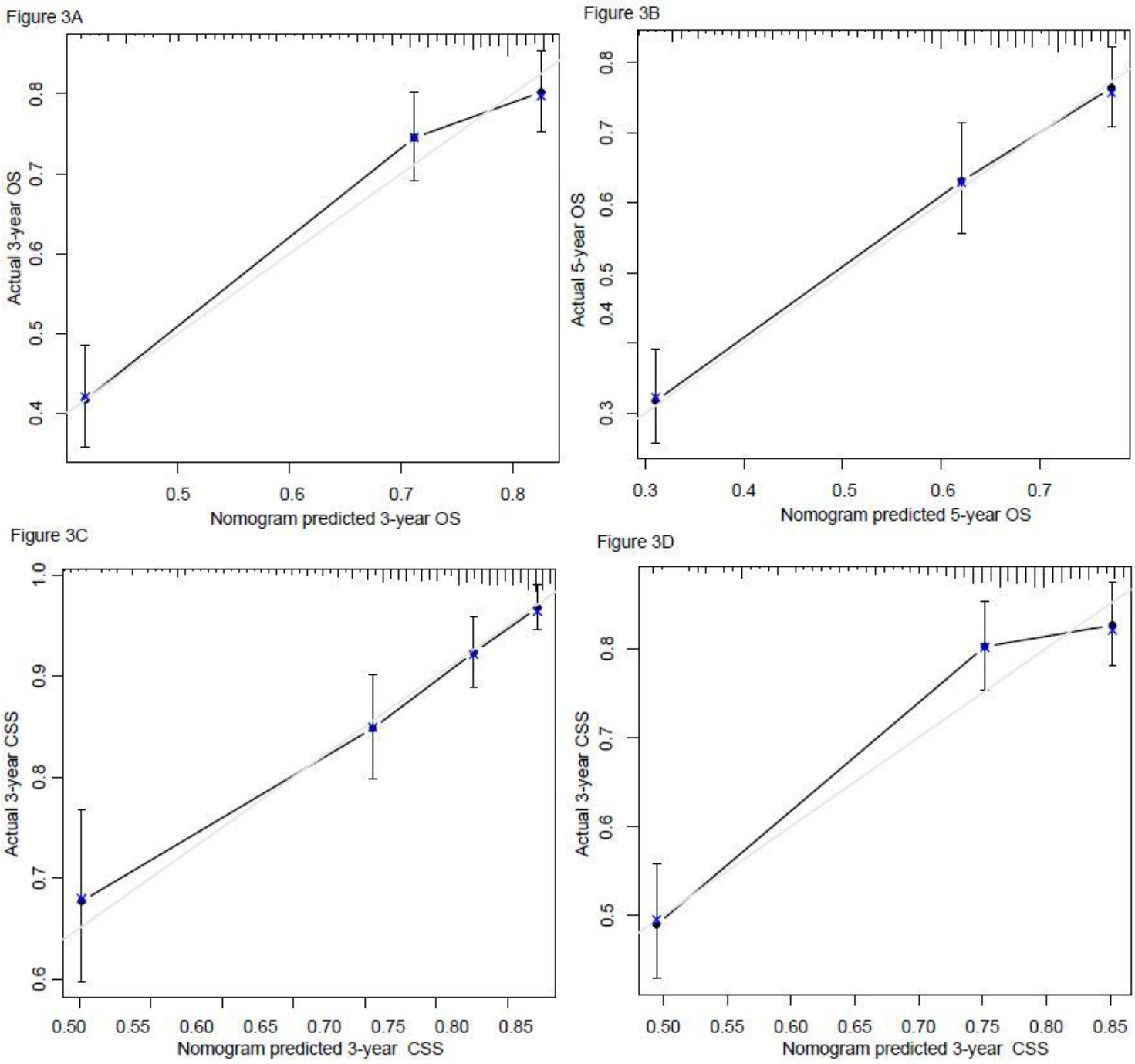


Figure 3

Calibration curves of nomograms in locally advanced OSCC patients in the training cohort. (A) 3-year OS; (B) 5-year OS; (C) 3-year CSS; (D)5-year CSS. OS, overall survival; CSS, cancer specific survival.

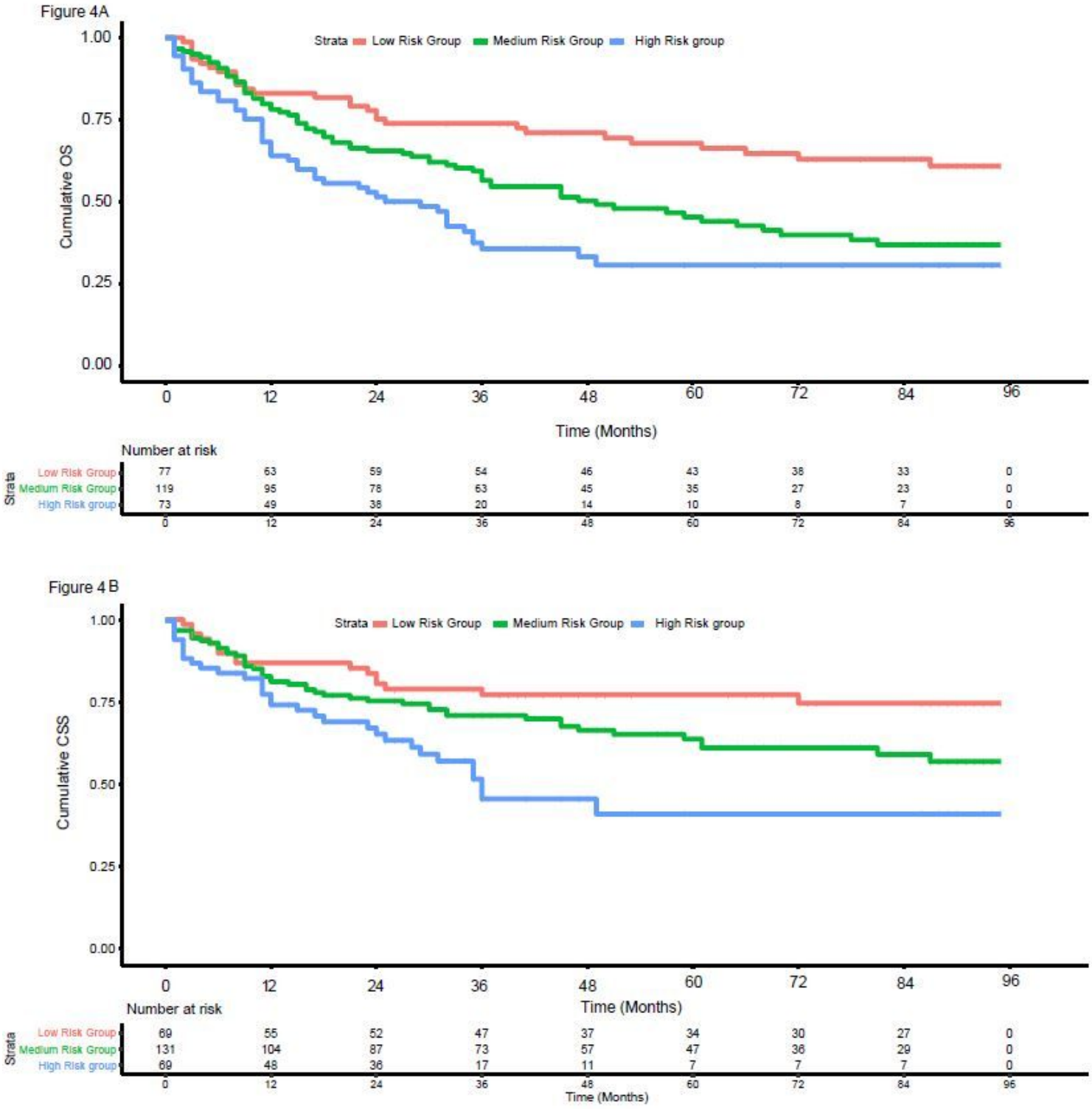


Figure 4

Kaplan-Meier survival curves and risk group stratification within all the patients based on the quartiles of nomograms predictions. (A) OS; (B) CSS. OS, overall survival; CSS, cancer specific survival.

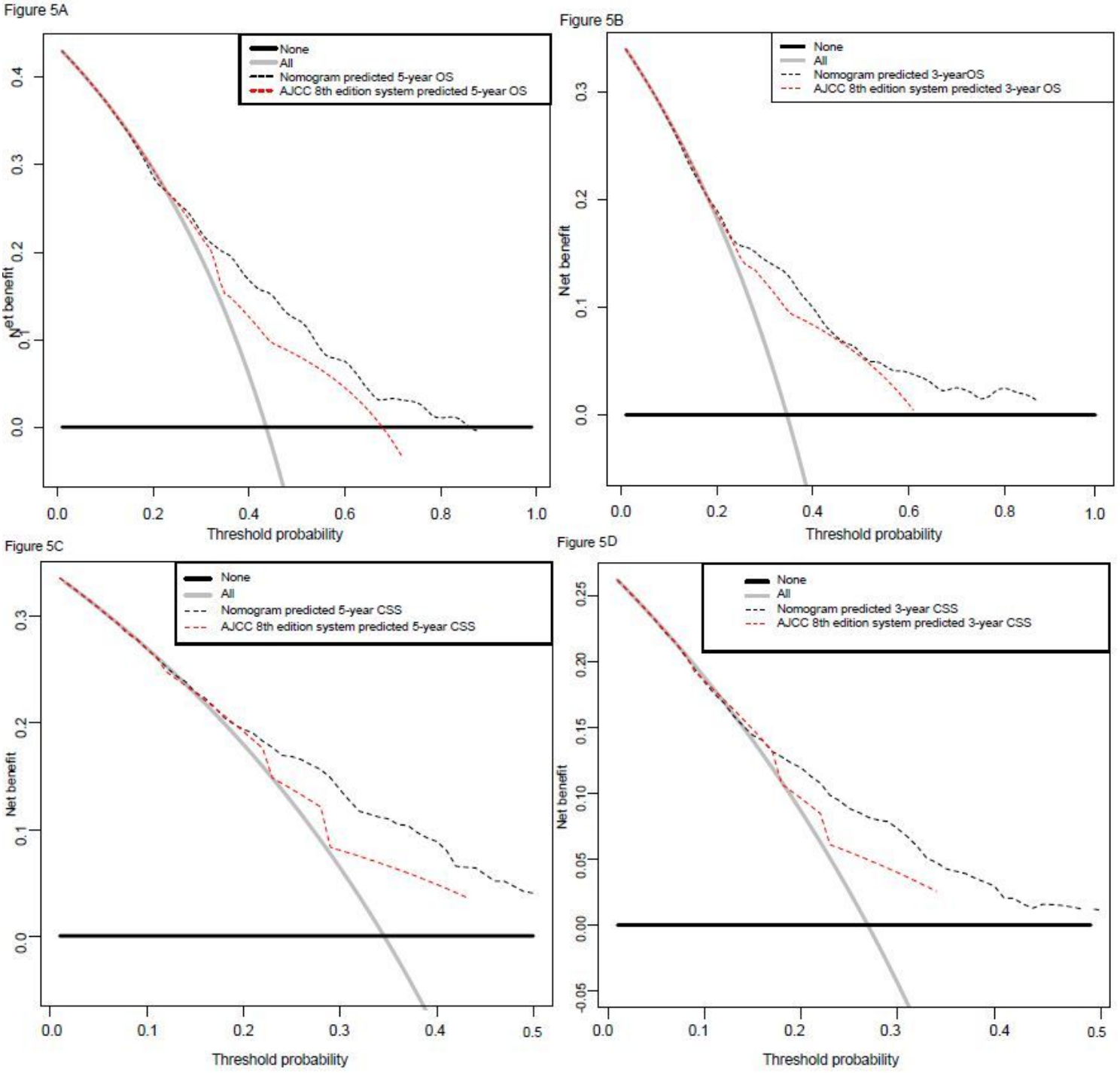


Figure 5

Decision curve analysis for the nomogram model and AJCC 8th staging system in the validation cohort. (A) 3-year OS; (B) 5-year OS; (C) 3-year CSS; (D)5-year CSS. AJCC: American Joint Committee on Cancer; OS, overall survival; CSS, cancer specific survival.

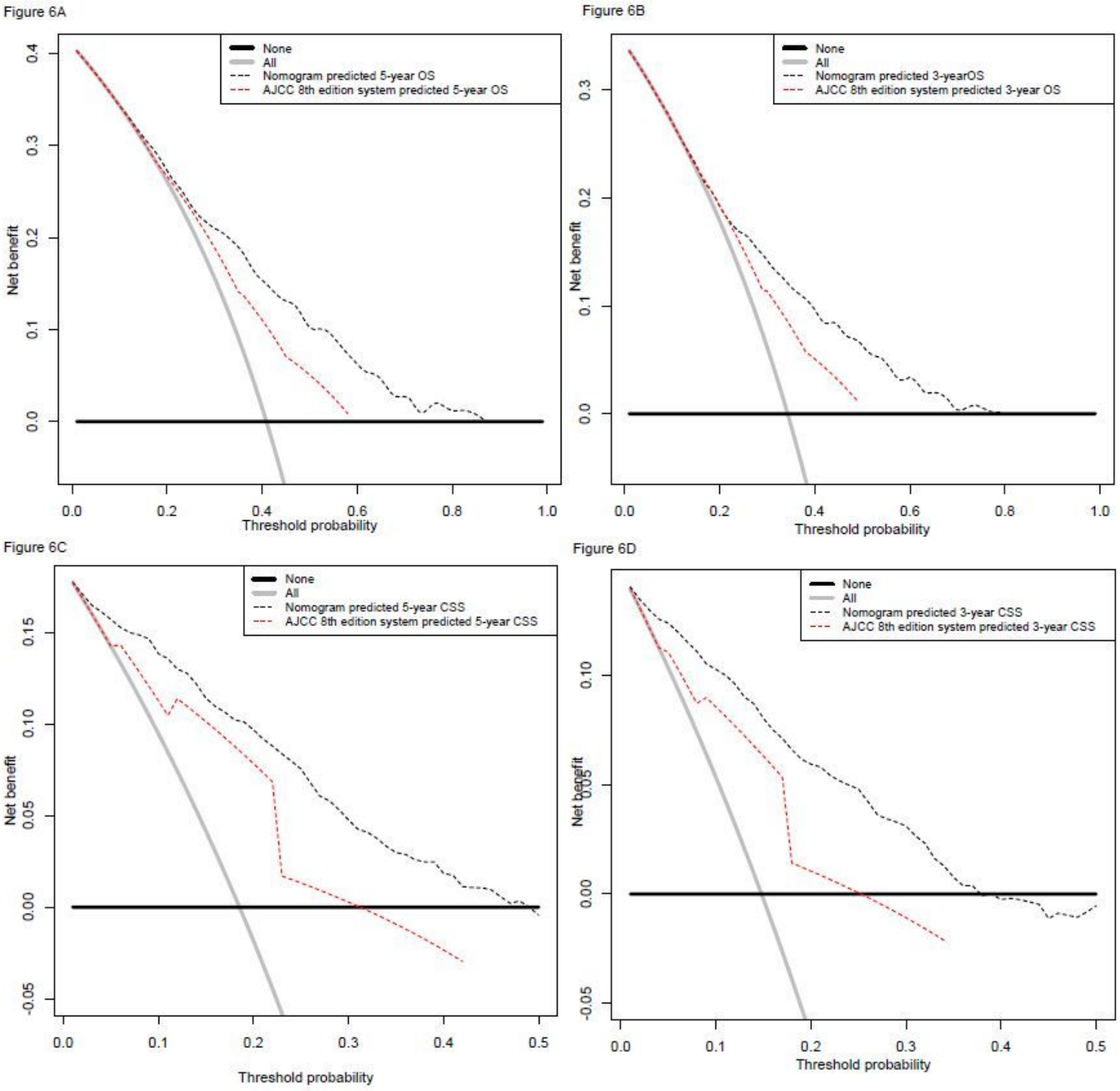


Figure 6

Decision curve analysis for the nomogram model and AJCC 8th staging system in the training cohort. (A) 3-year OS; (B) 5-year OS; (C) 3-year CSS; (D)5-year CSS. AJCC: American Joint Committee on Cancer; OS, overall survival; CSS, cancer specific survival.